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(54) **SPIROCYCLIC DEGRONIMERS FOR TARGET PROTEIN DEGRADATION**

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(51) **Int. Cl.**

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A61K 47/54	(2017.01)
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C07D 471/10	(2006.01)
C07D 519/00	(2006.01)
A61K 31/435	(2006.01)
A61K 31/438	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 47/545*** (2017.08); ***A61K 31/435*** (2013.01); ***A61K 31/438*** (2013.01); ***A61K 47/554*** (2017.08); ***C07D 471/10*** (2013.01); ***C07D 498/20*** (2013.01); ***C07D 519/00*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 47/545; A61P 35/00

See application file for complete search history.

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(57) **ABSTRACT**

This invention provides compounds that have spirocyclic E3 Ubiquitin Ligase targeting moieties (Degrons), which can be used as is or linked to a targeting ligand for a protein that has been selected for in vivo degradation, and methods of use and compositions thereof as well as methods for their preparation.

26 Claims, 389 Drawing Sheets

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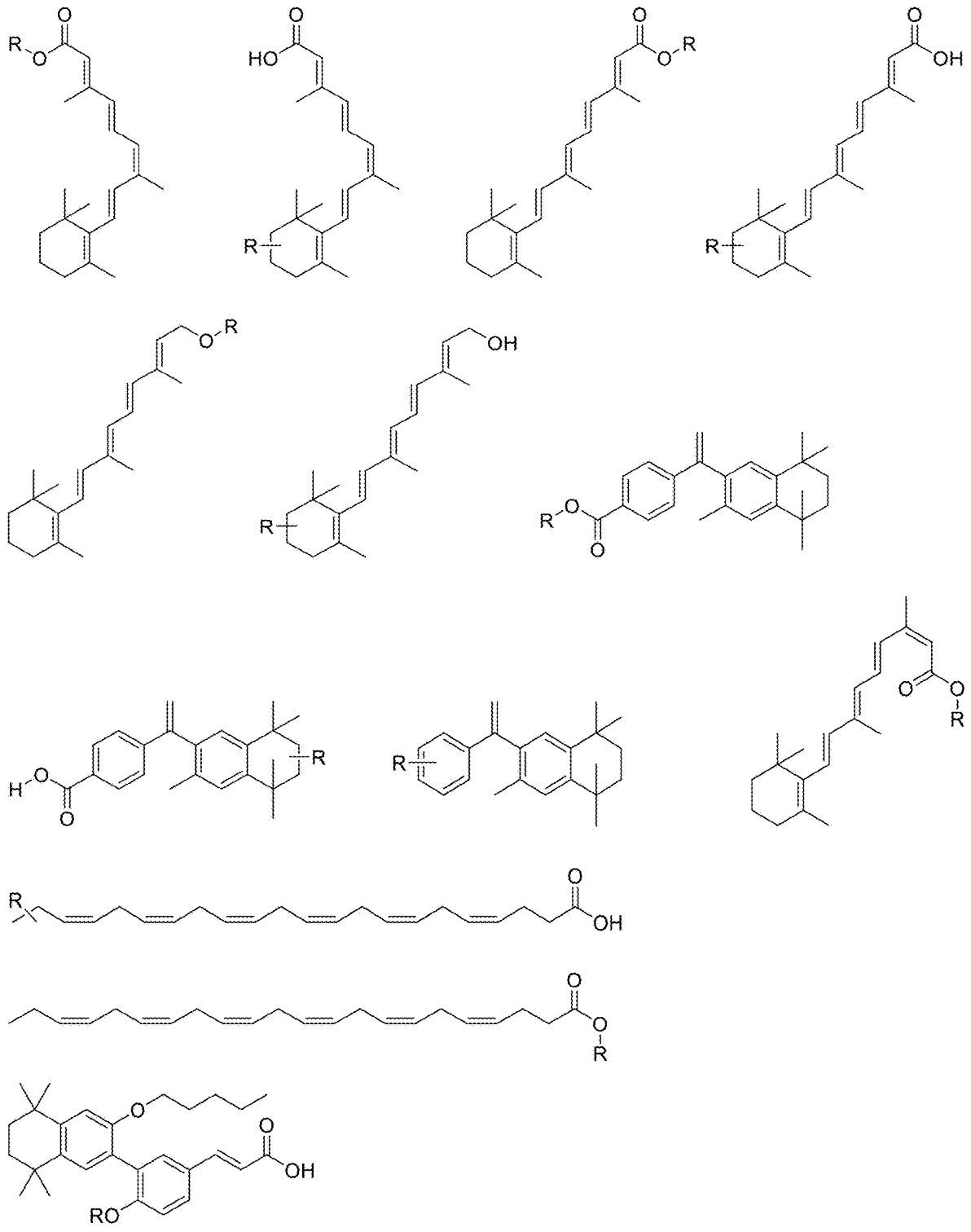
FIG. 1A



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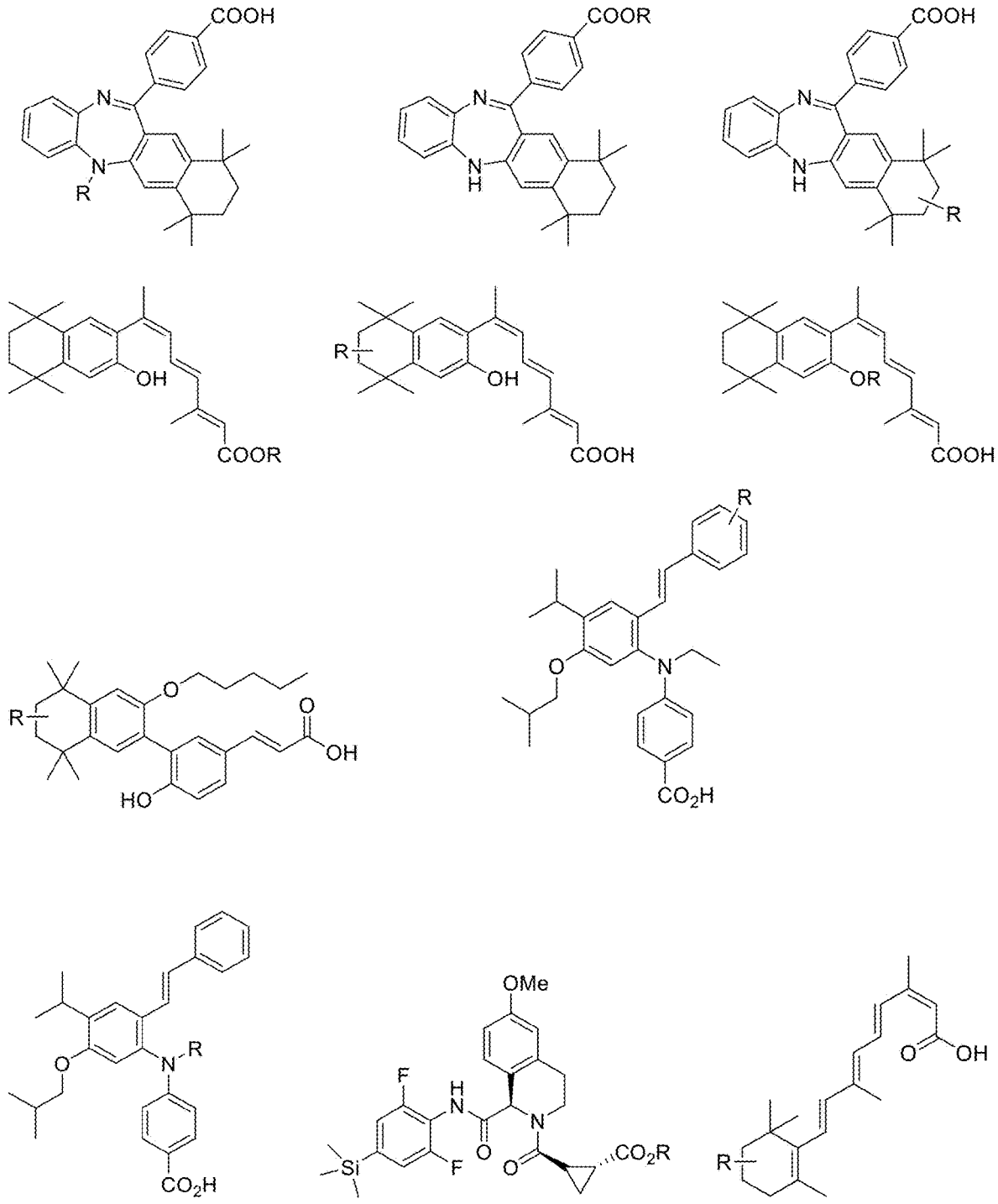
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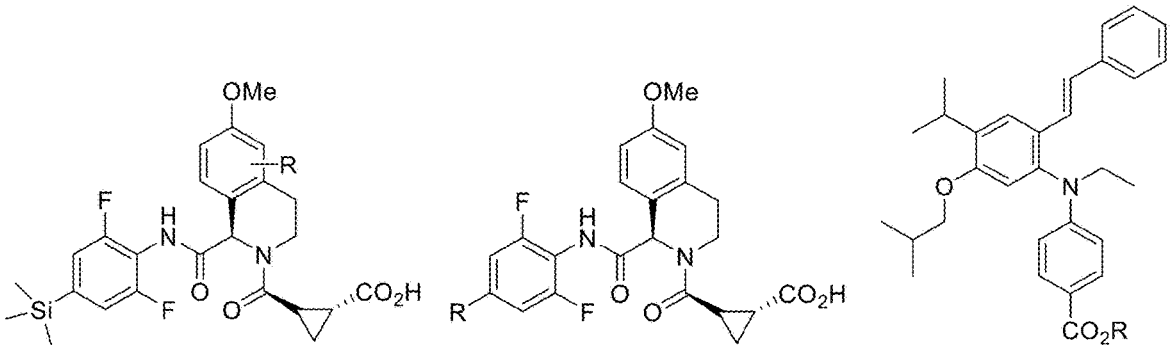
FIG. 1C



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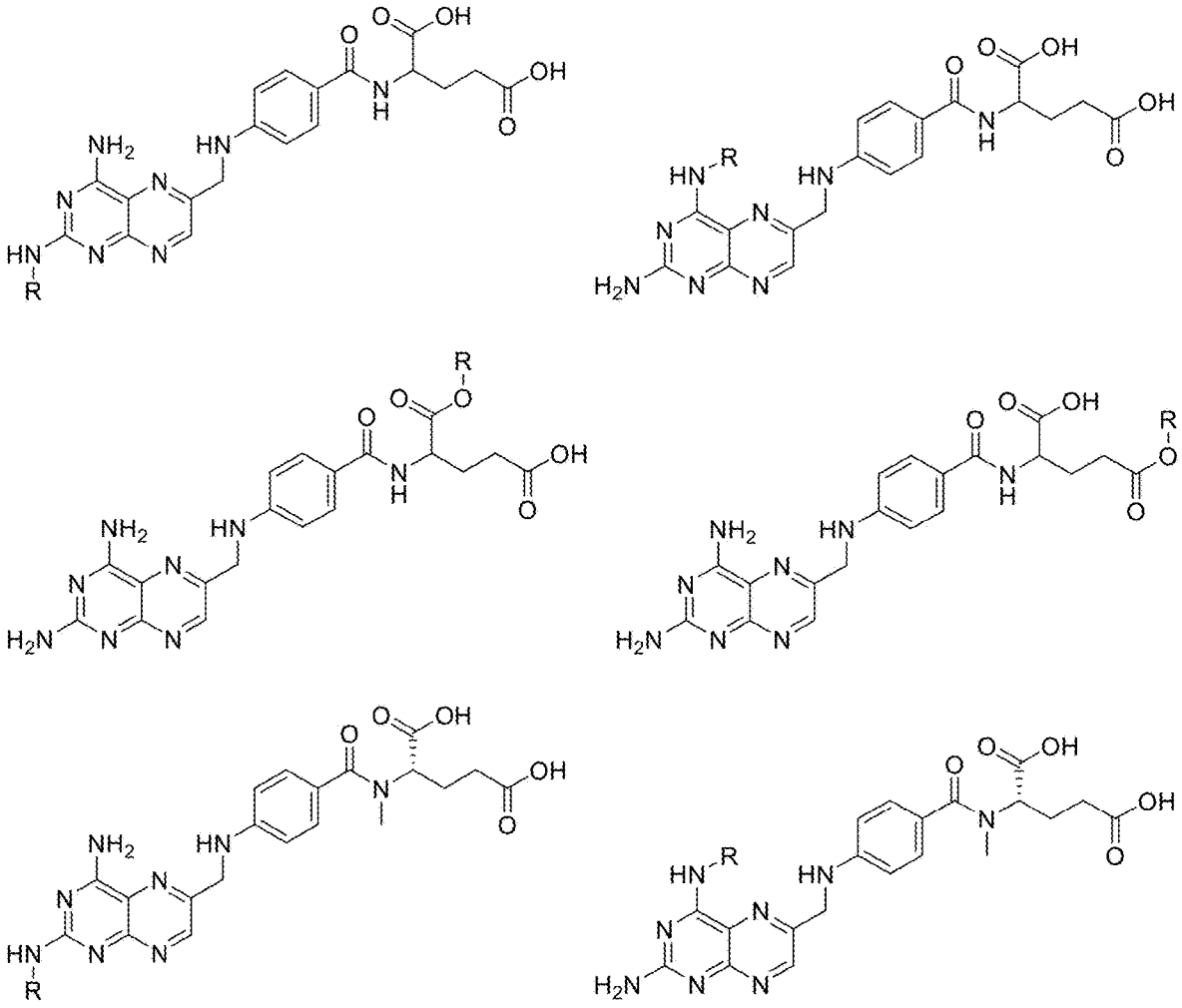
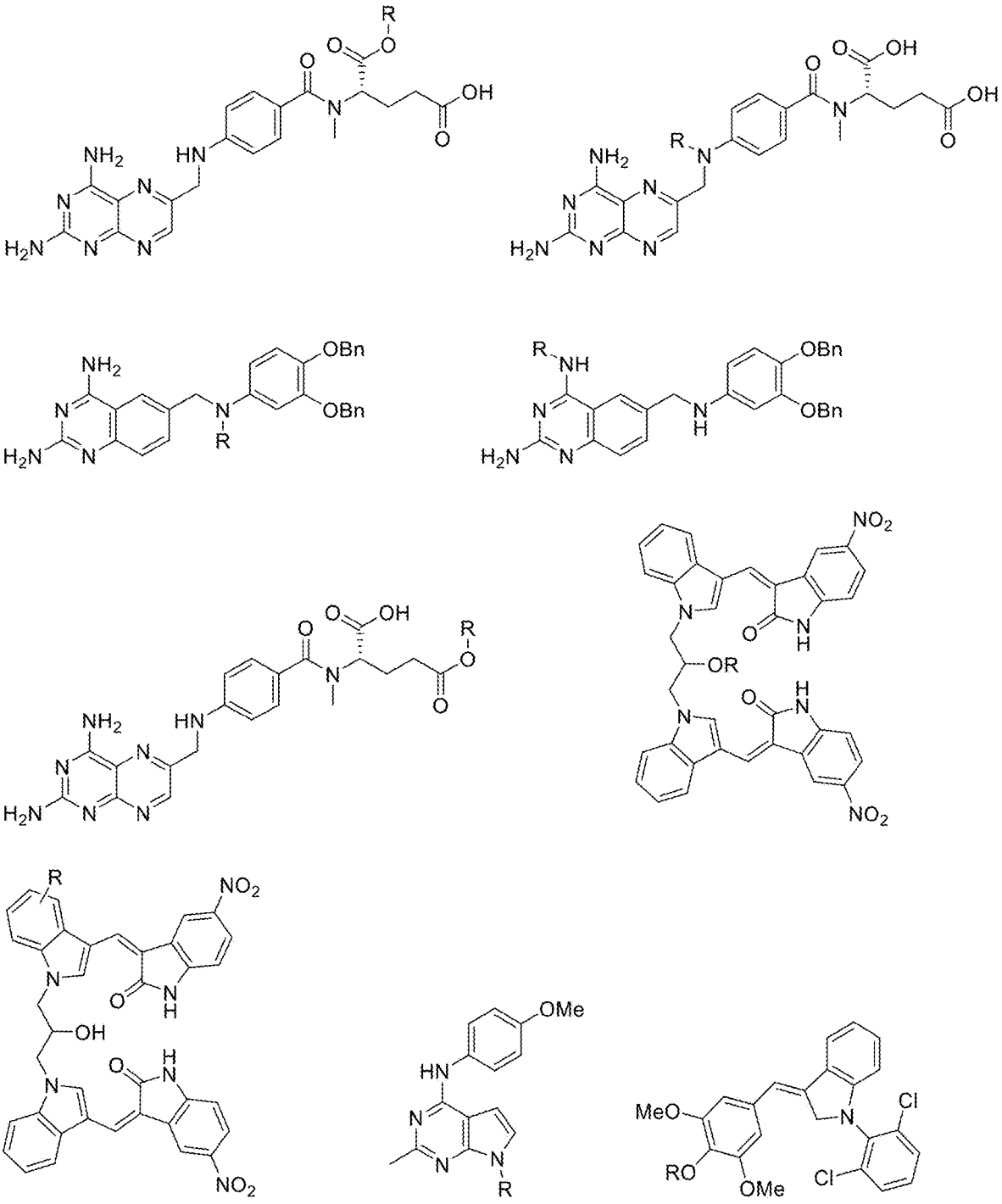


FIG. 1E



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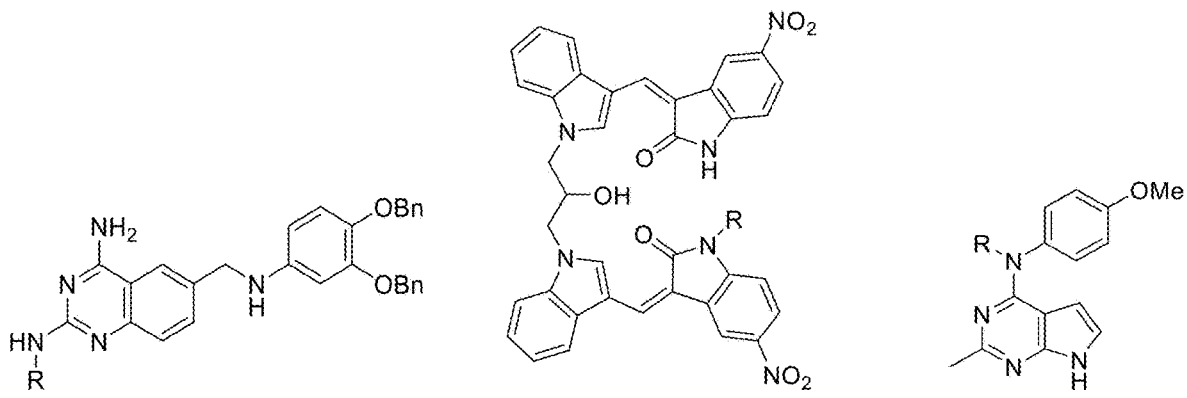


FIG. 1G

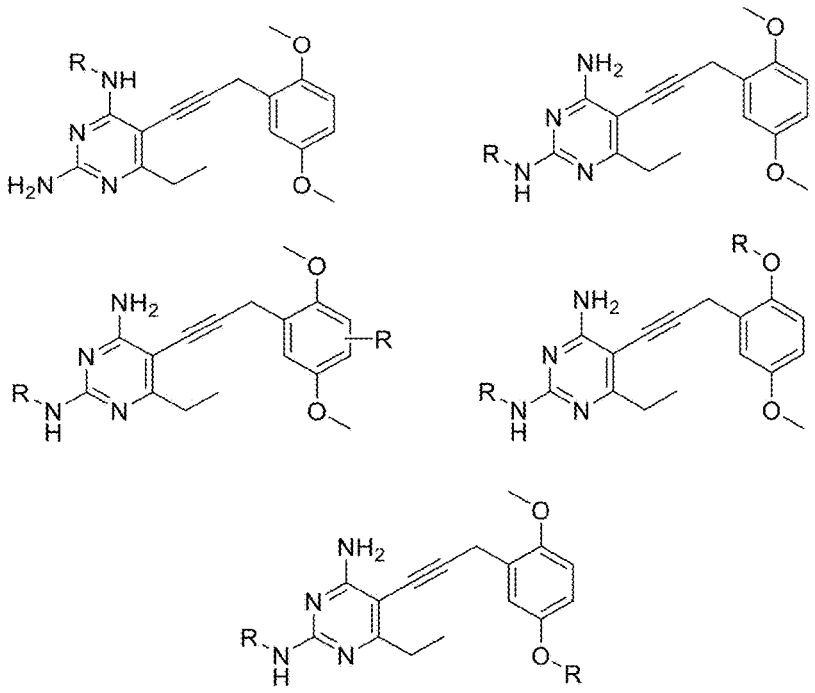


FIG. 1H

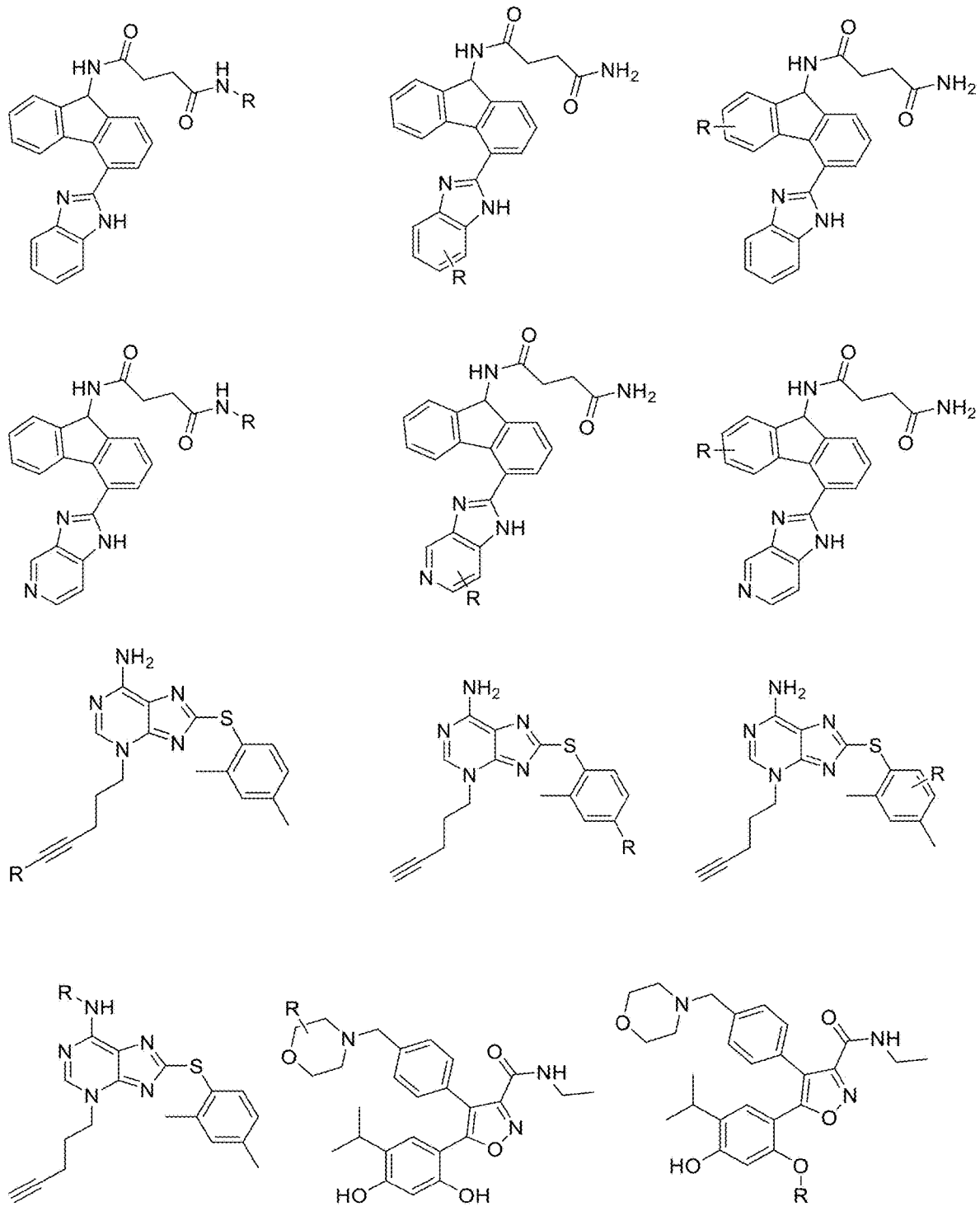


FIG. 1I

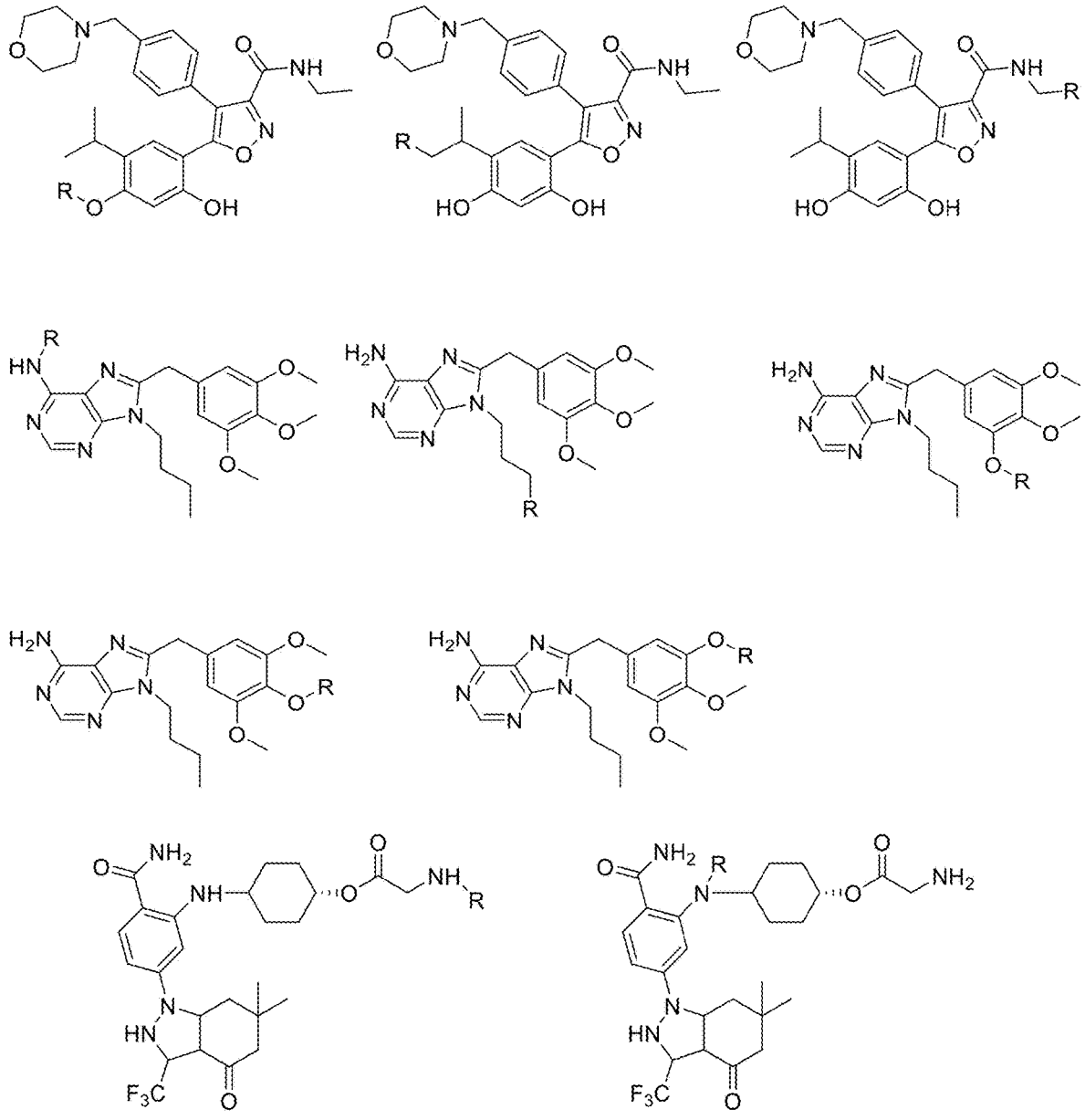
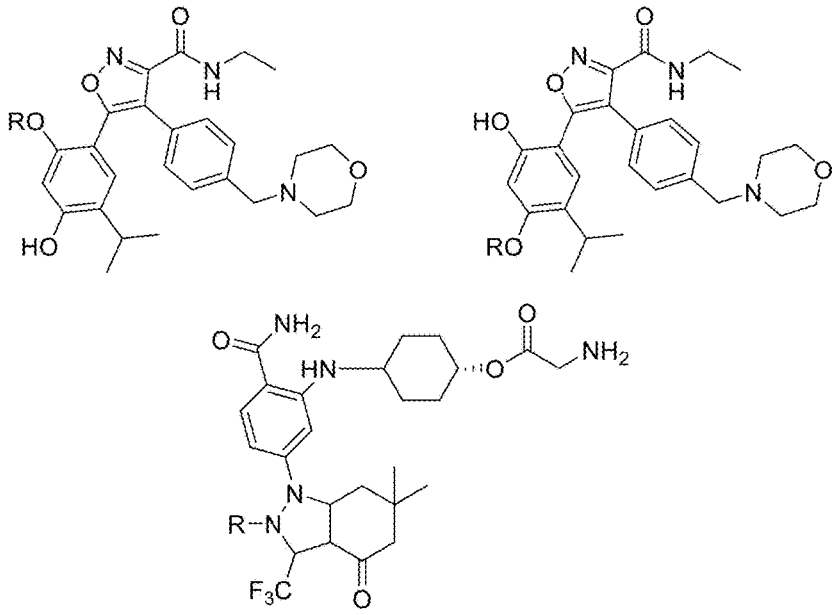


FIG. 1J



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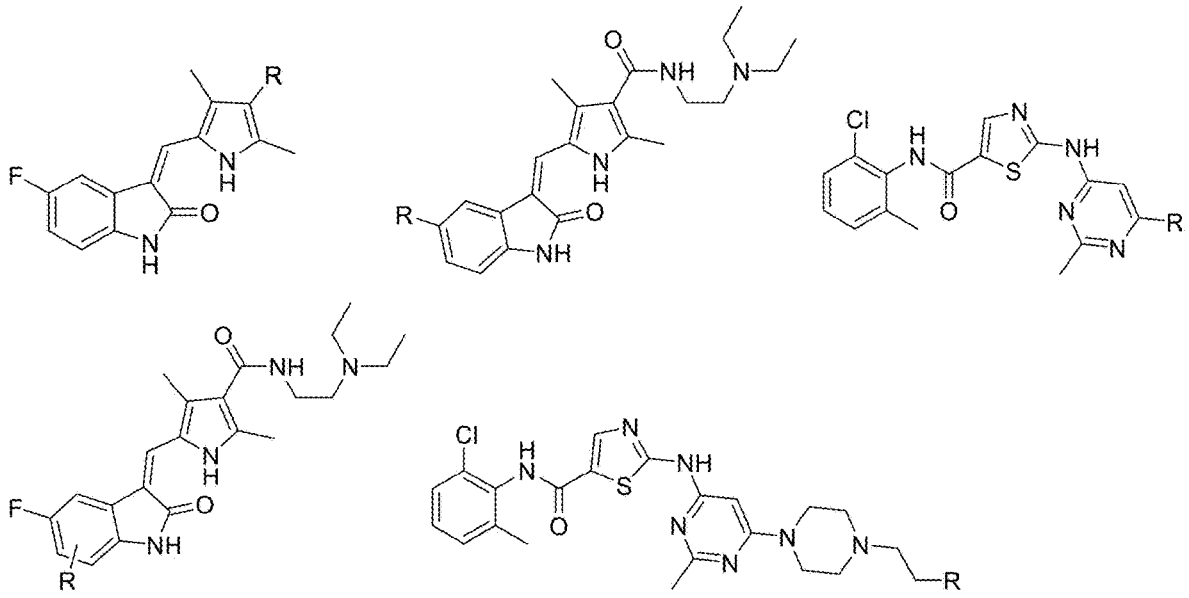


FIG. 1L

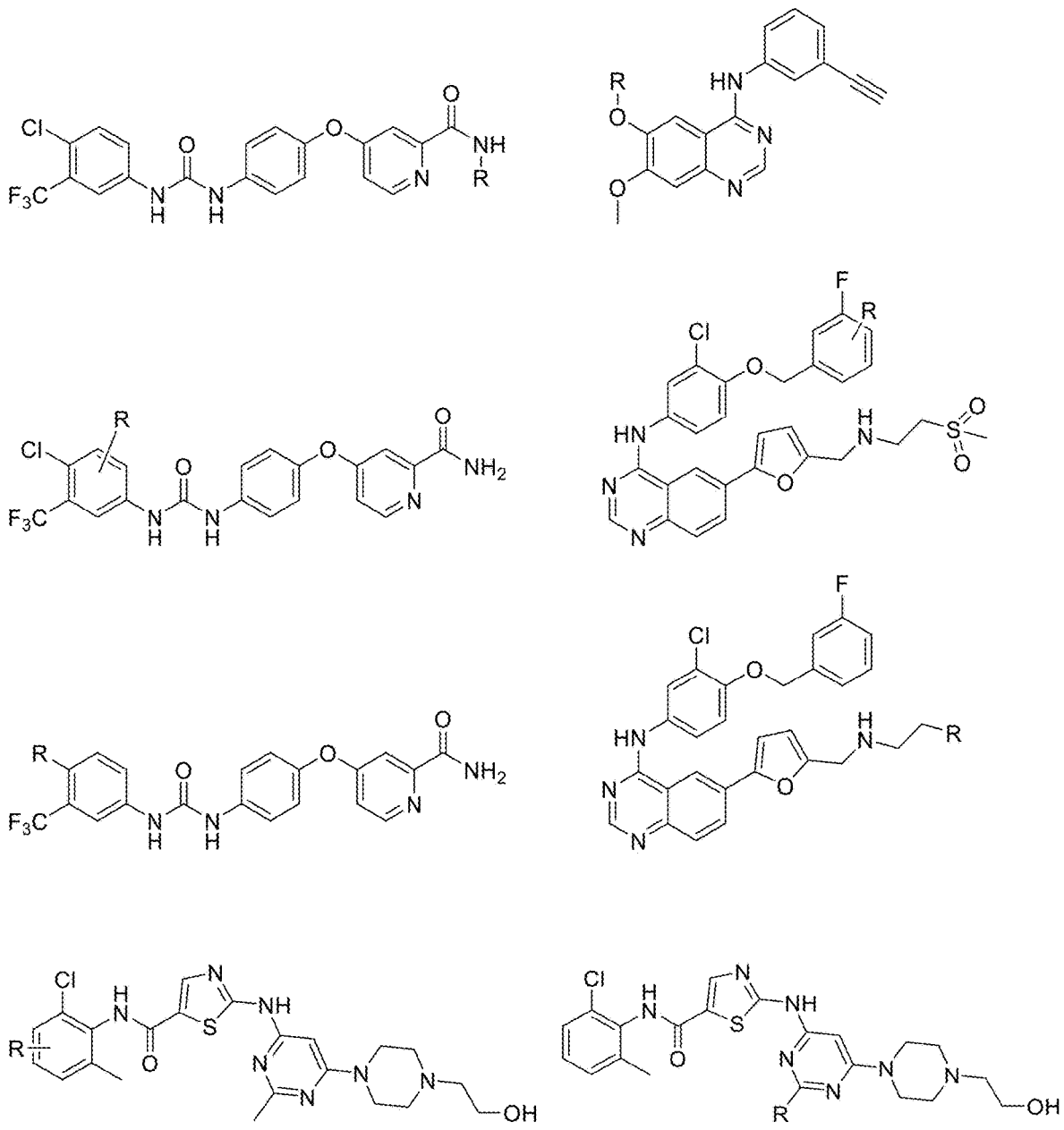


FIG. 1M

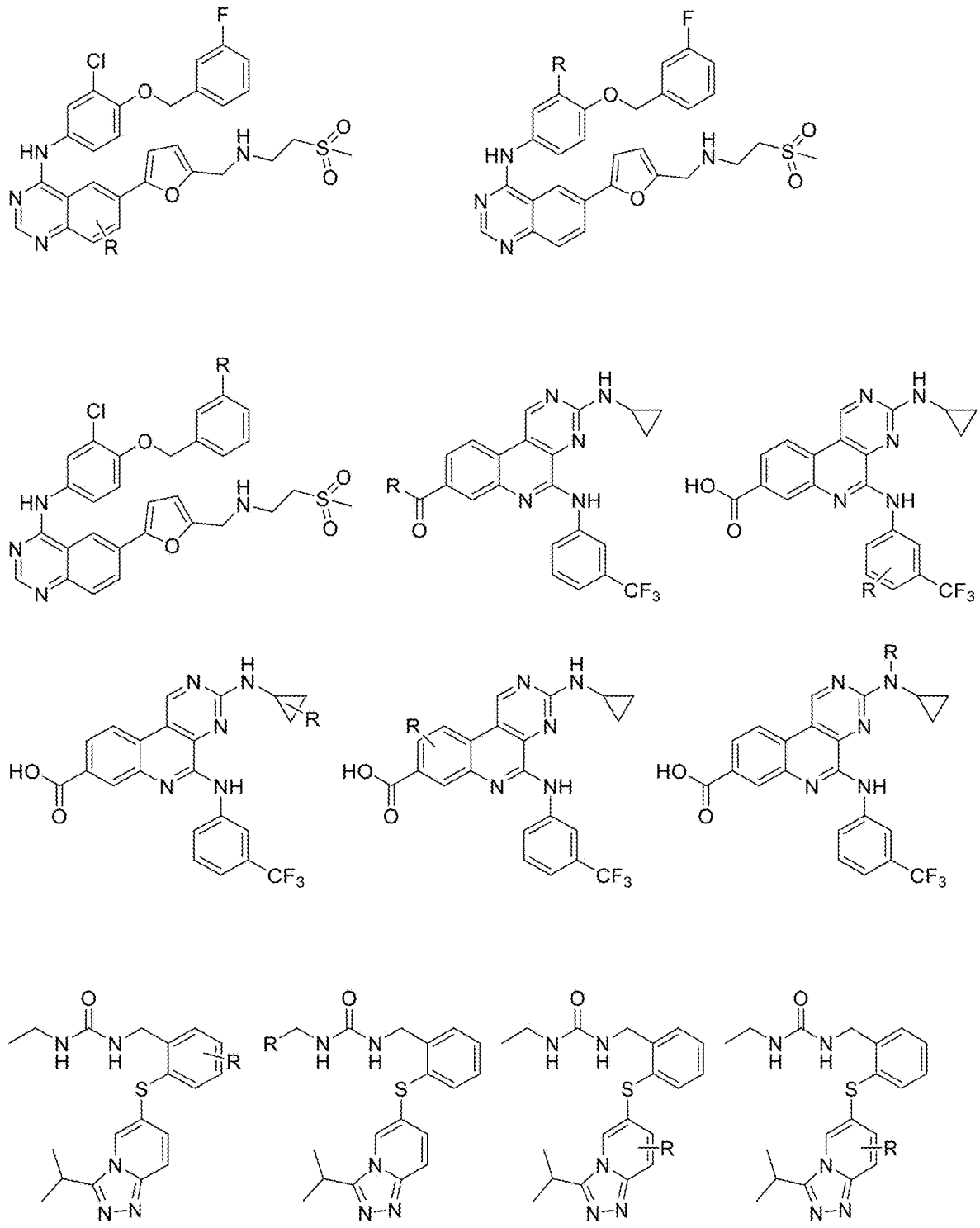


FIG. 1N

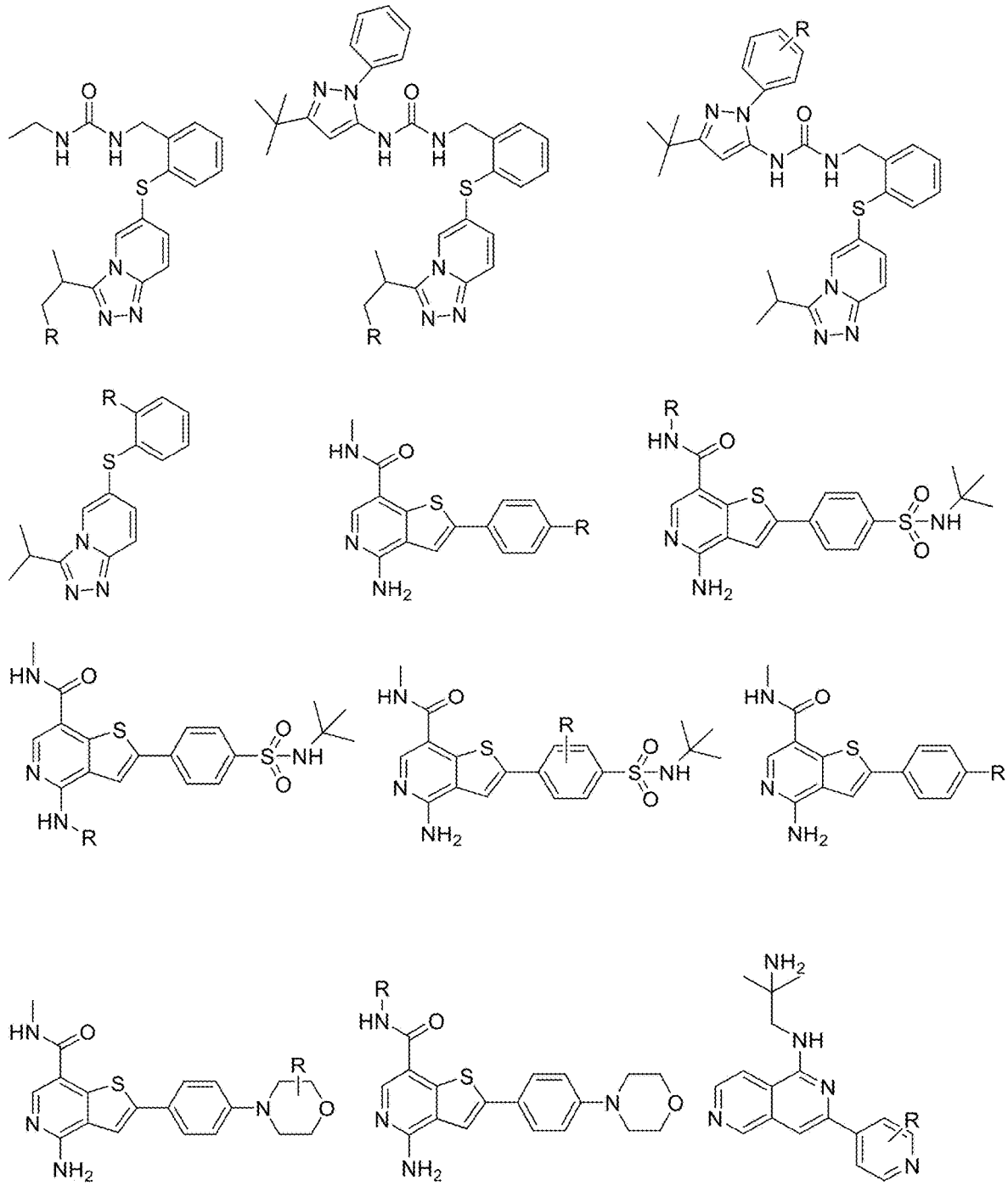


FIG. 1O

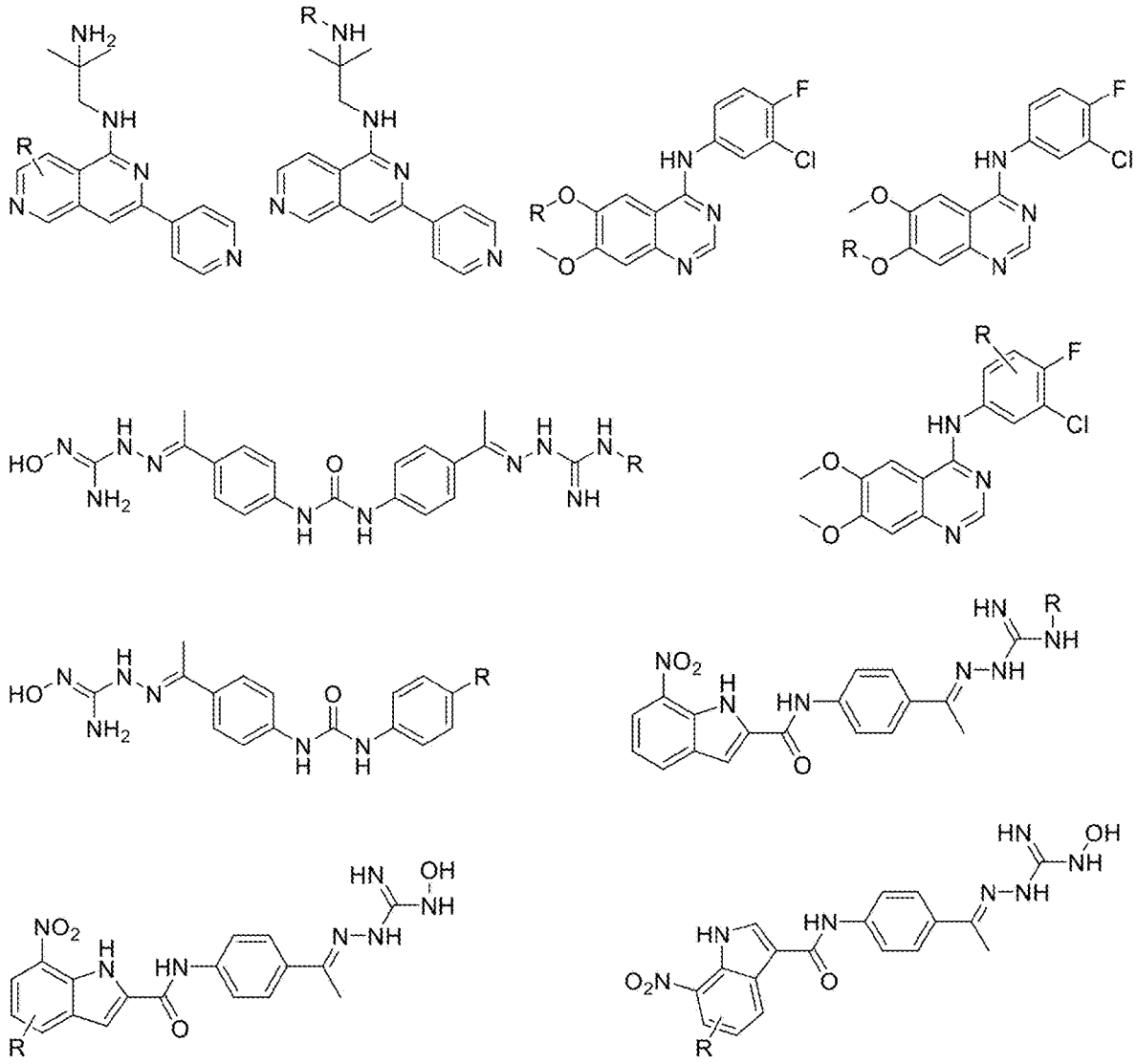


FIG. 1P

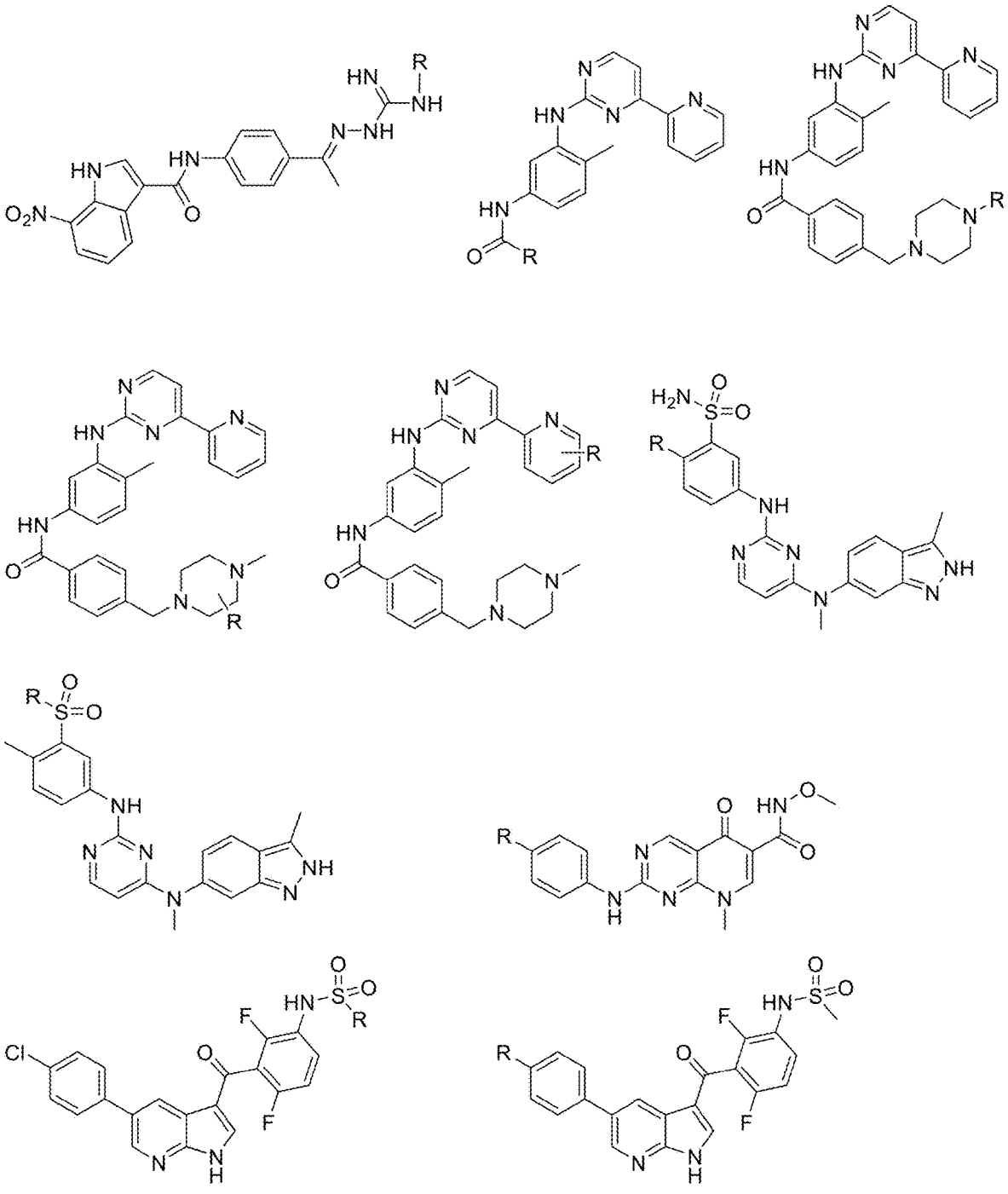


FIG. 1Q

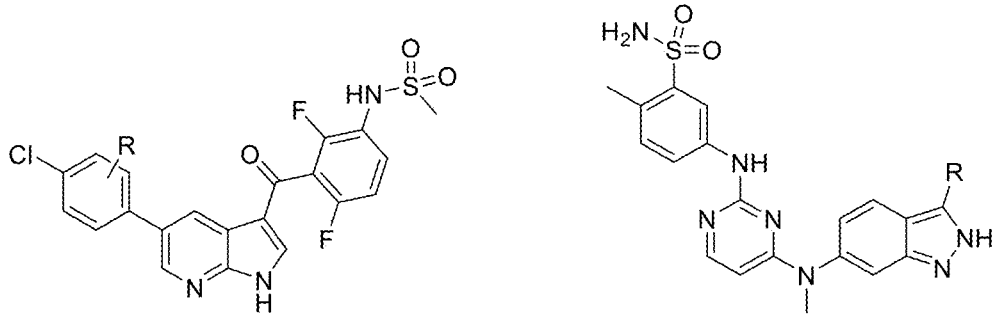


FIG. 1R

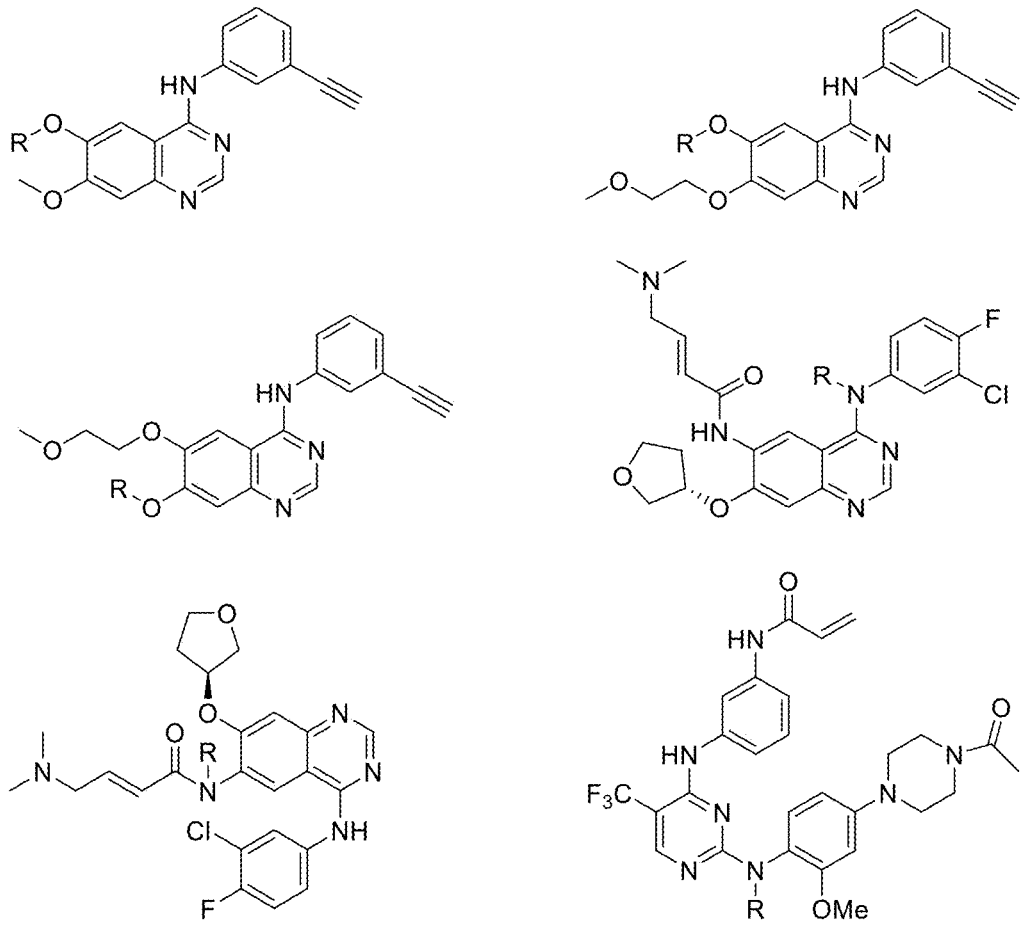


FIG. 1S

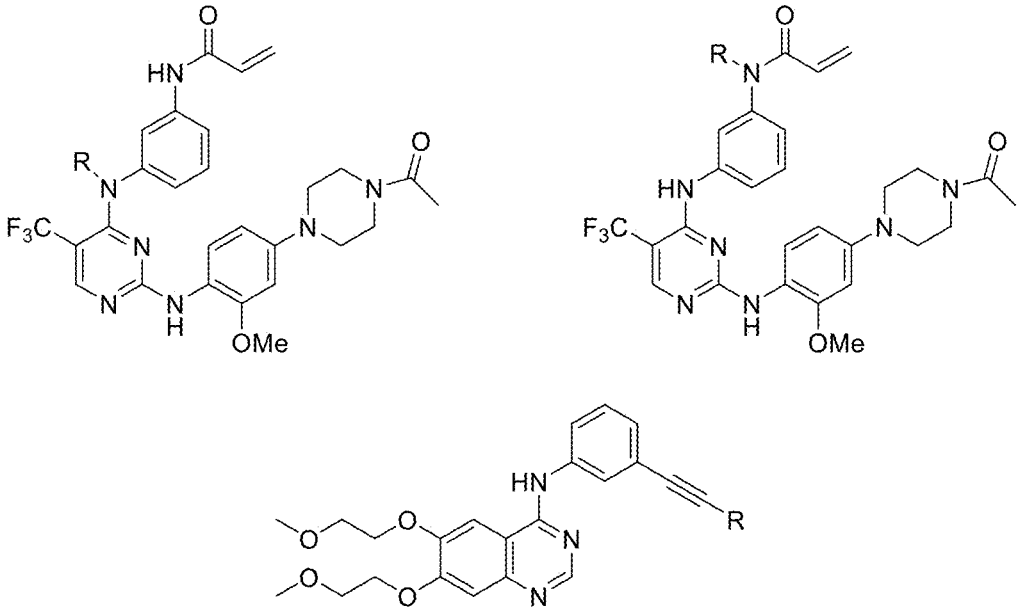


FIG. 1T

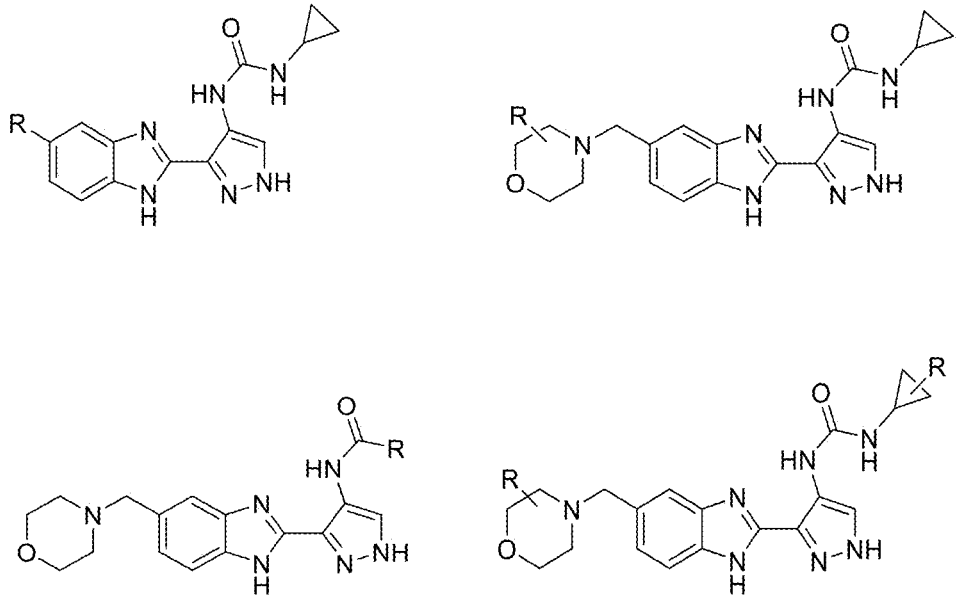


FIG. 1U

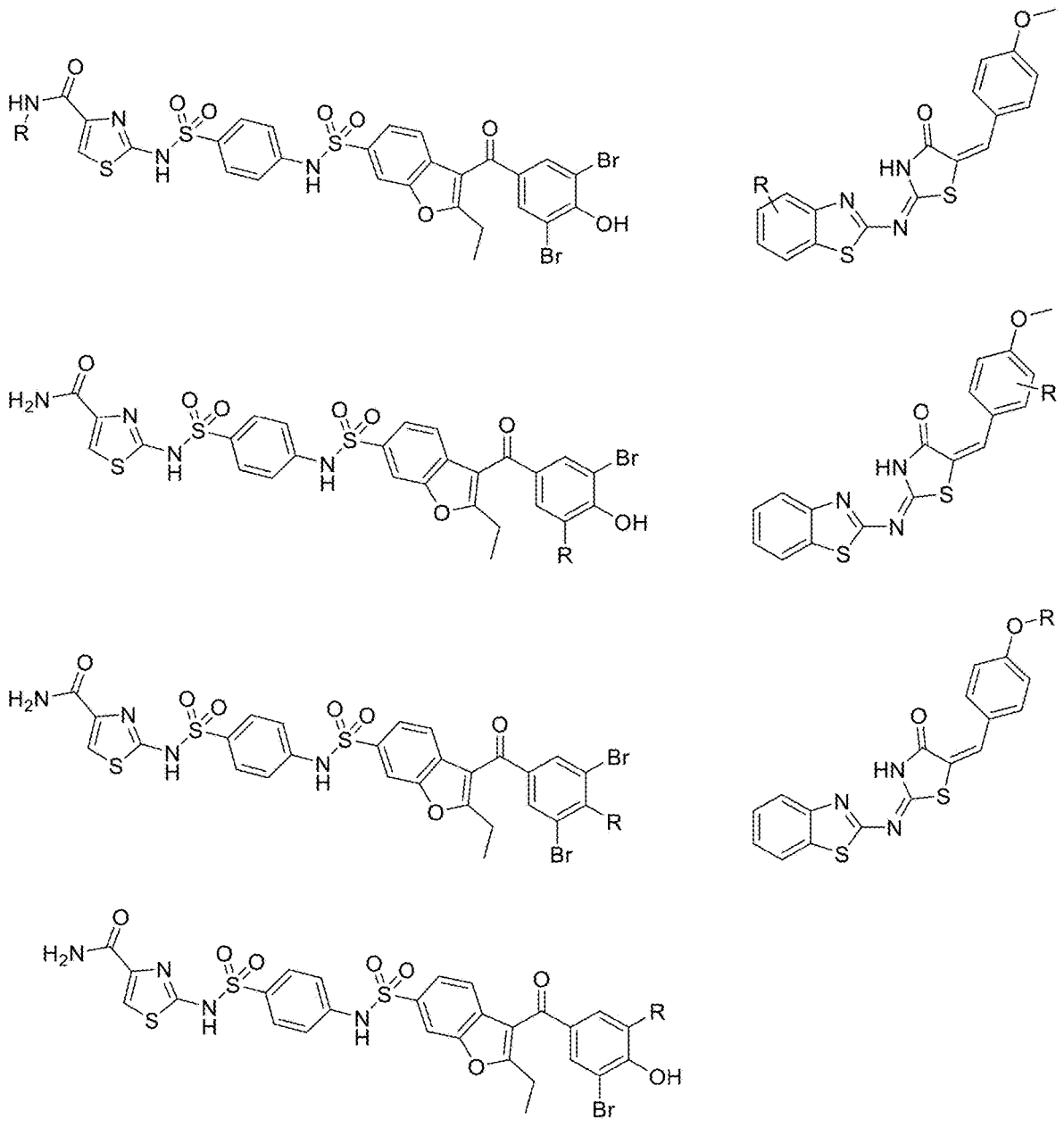


FIG. 1V

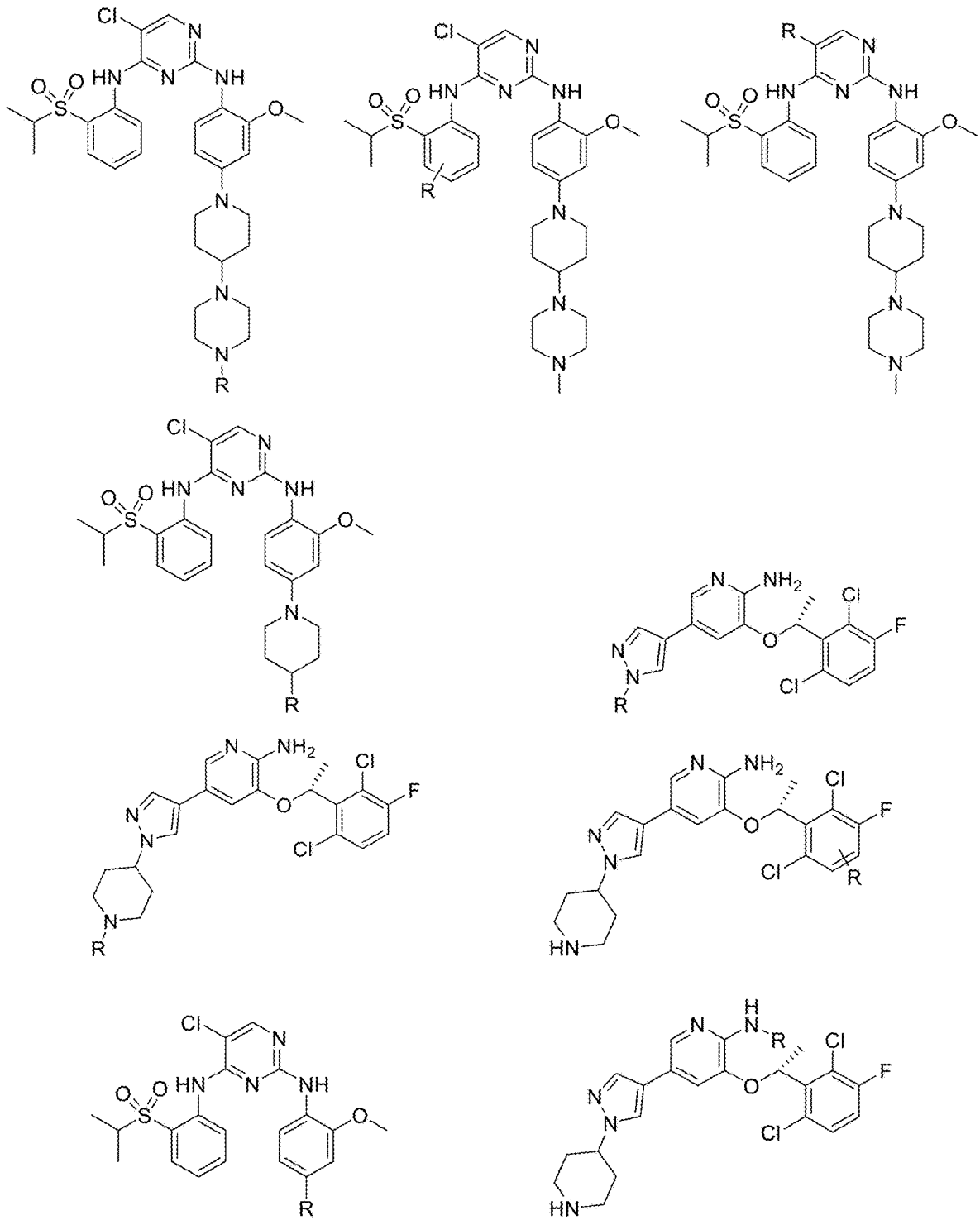


FIG. 1W

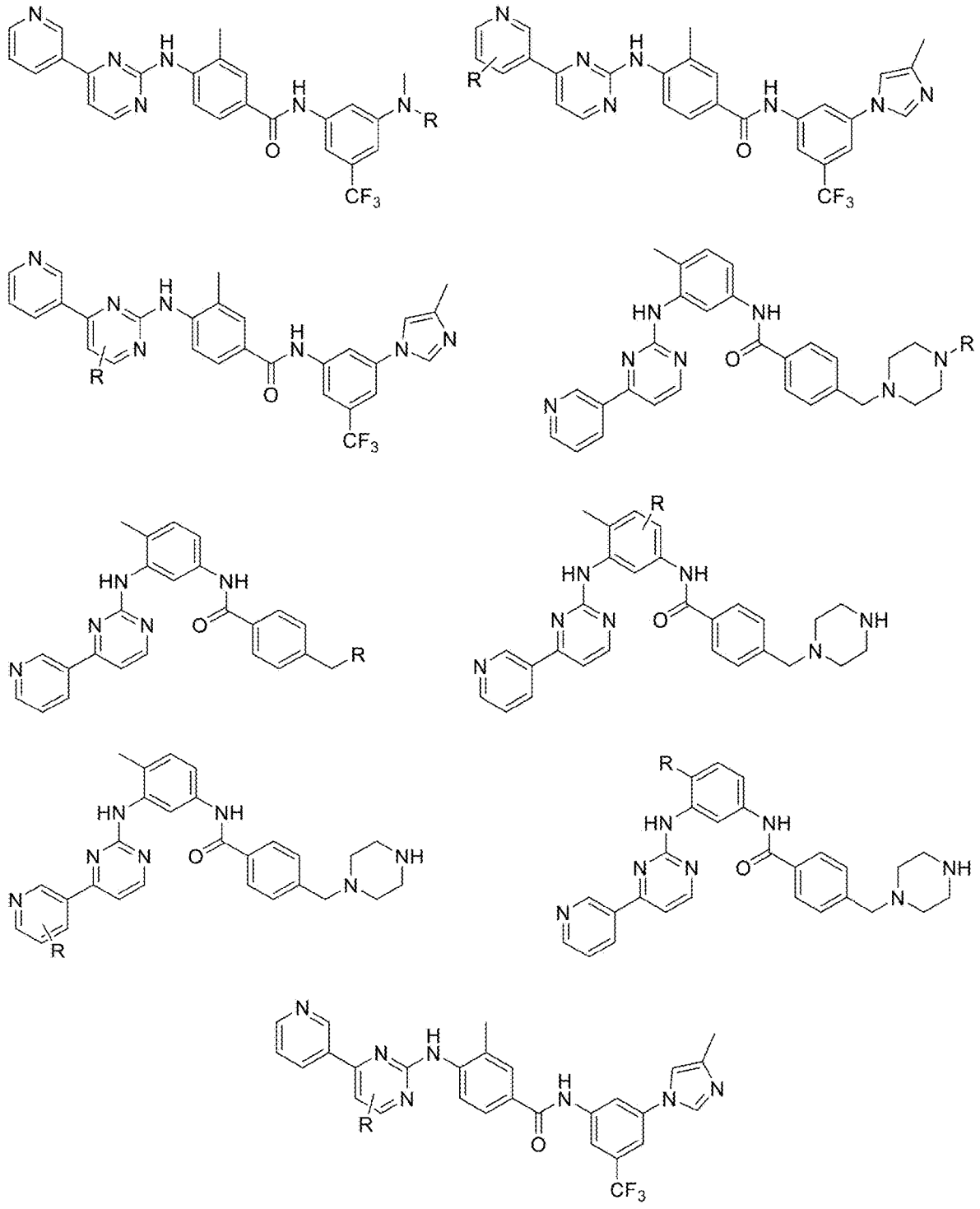


FIG. 1X

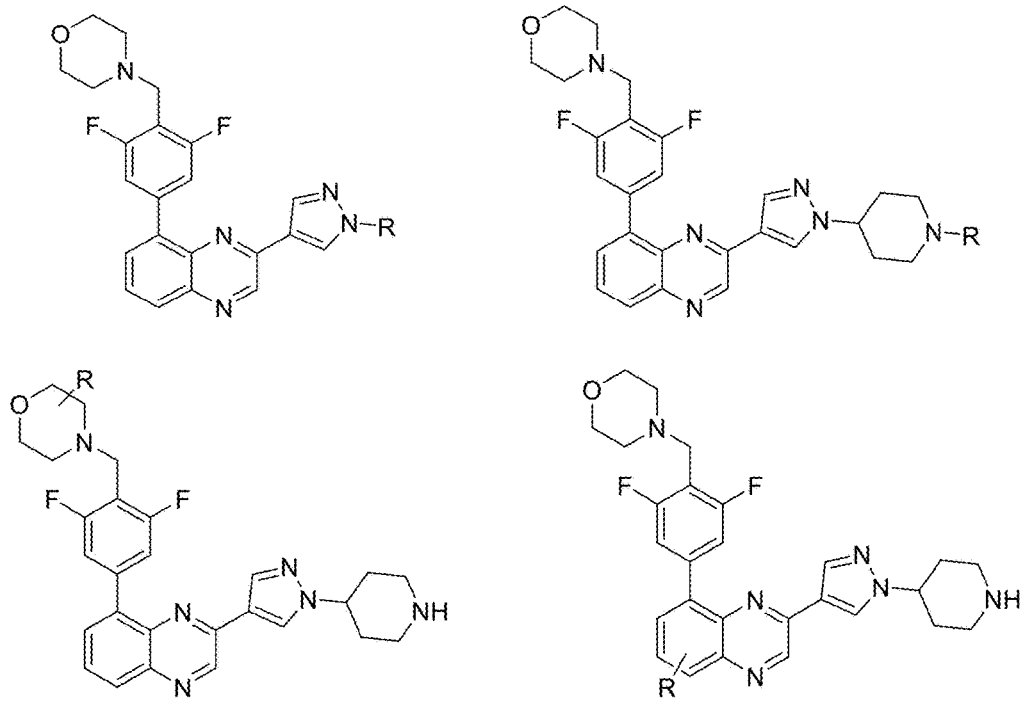


FIG. 1Y

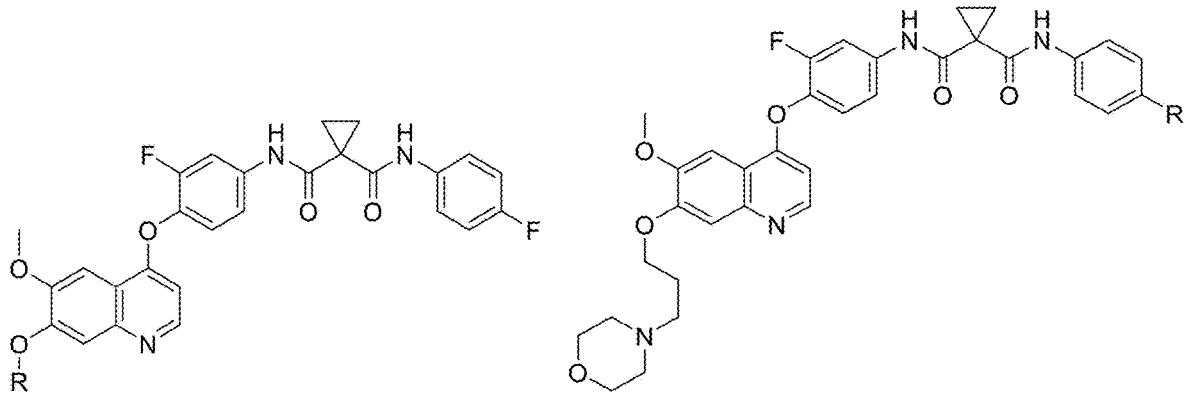


FIG. 1Z

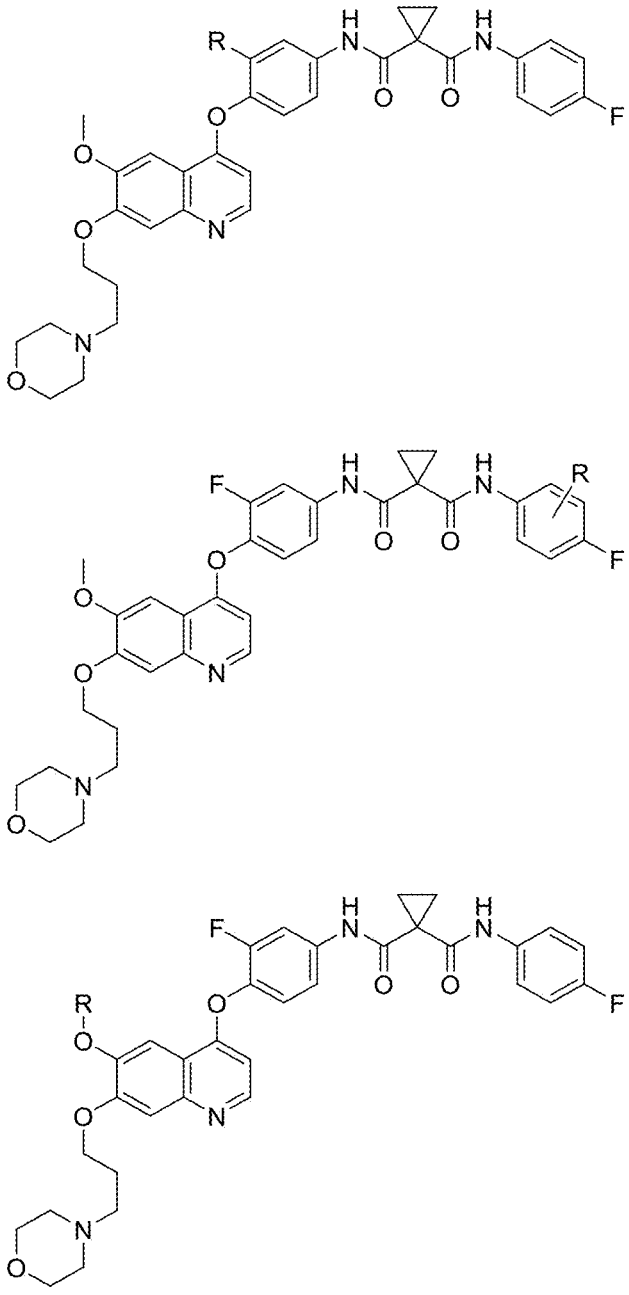


FIG. 1AA

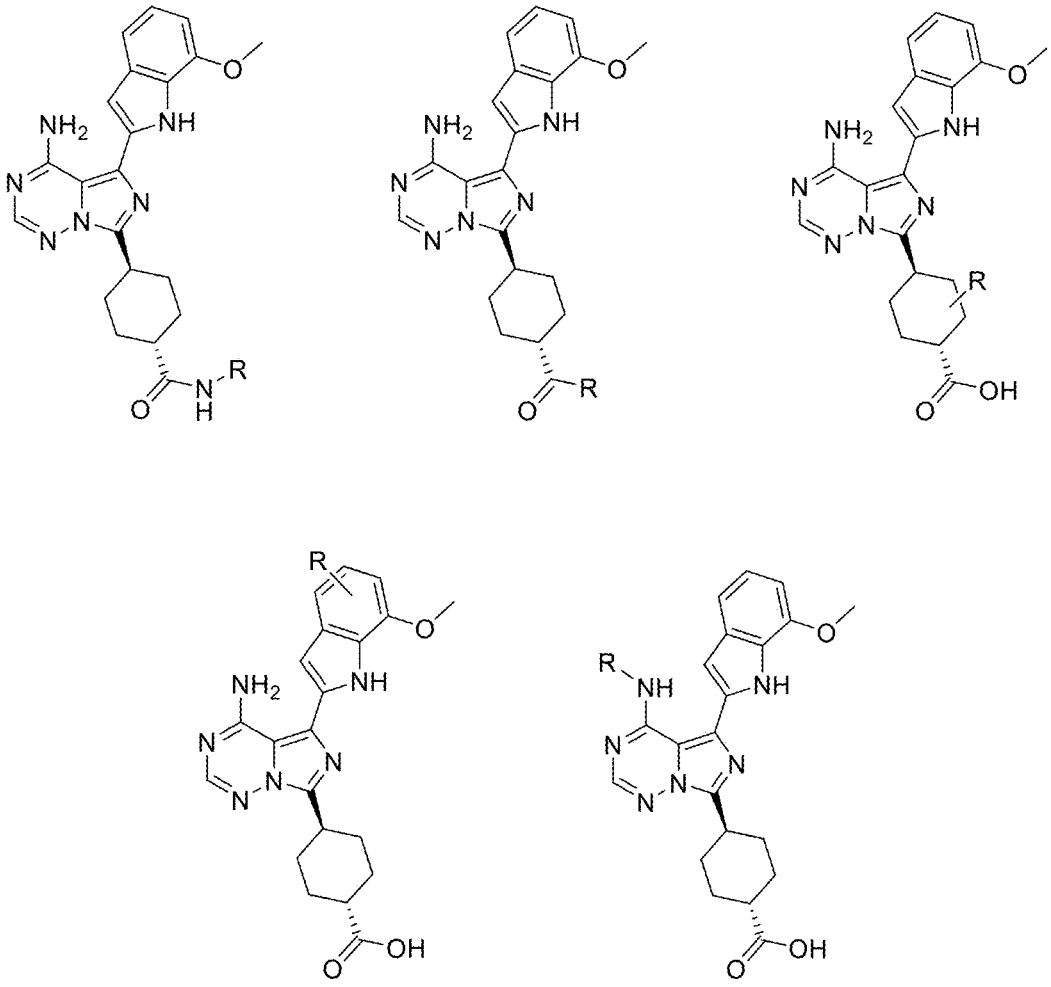


FIG. 1BB

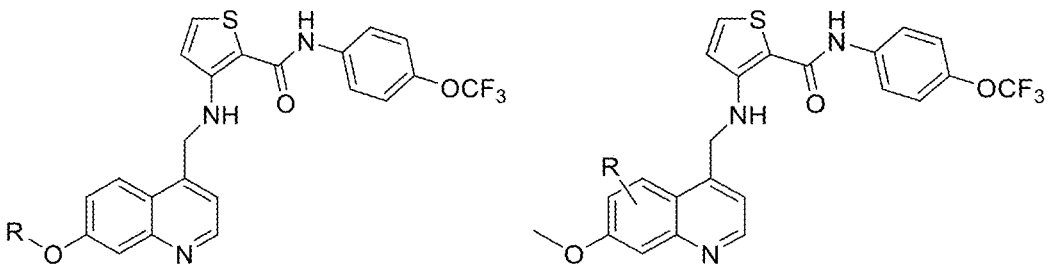


FIG. 1CC

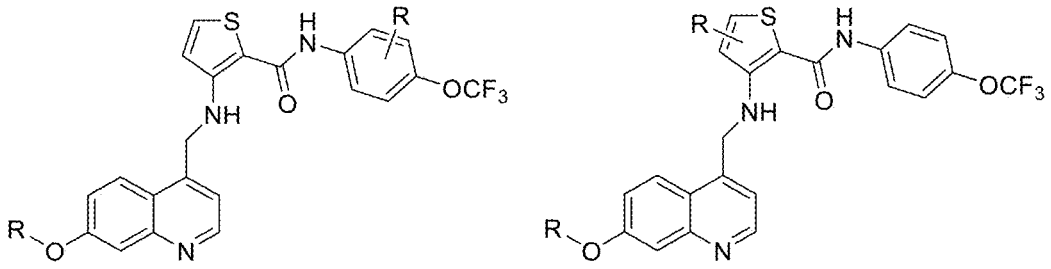


FIG. 1DD

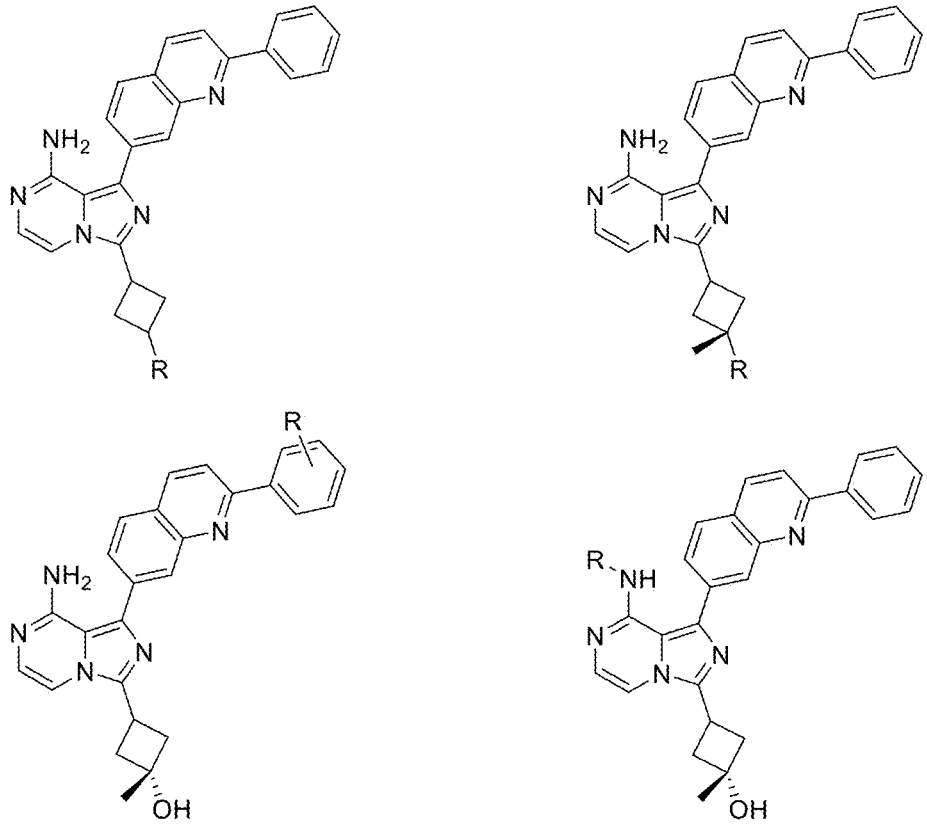


FIG. 1EE

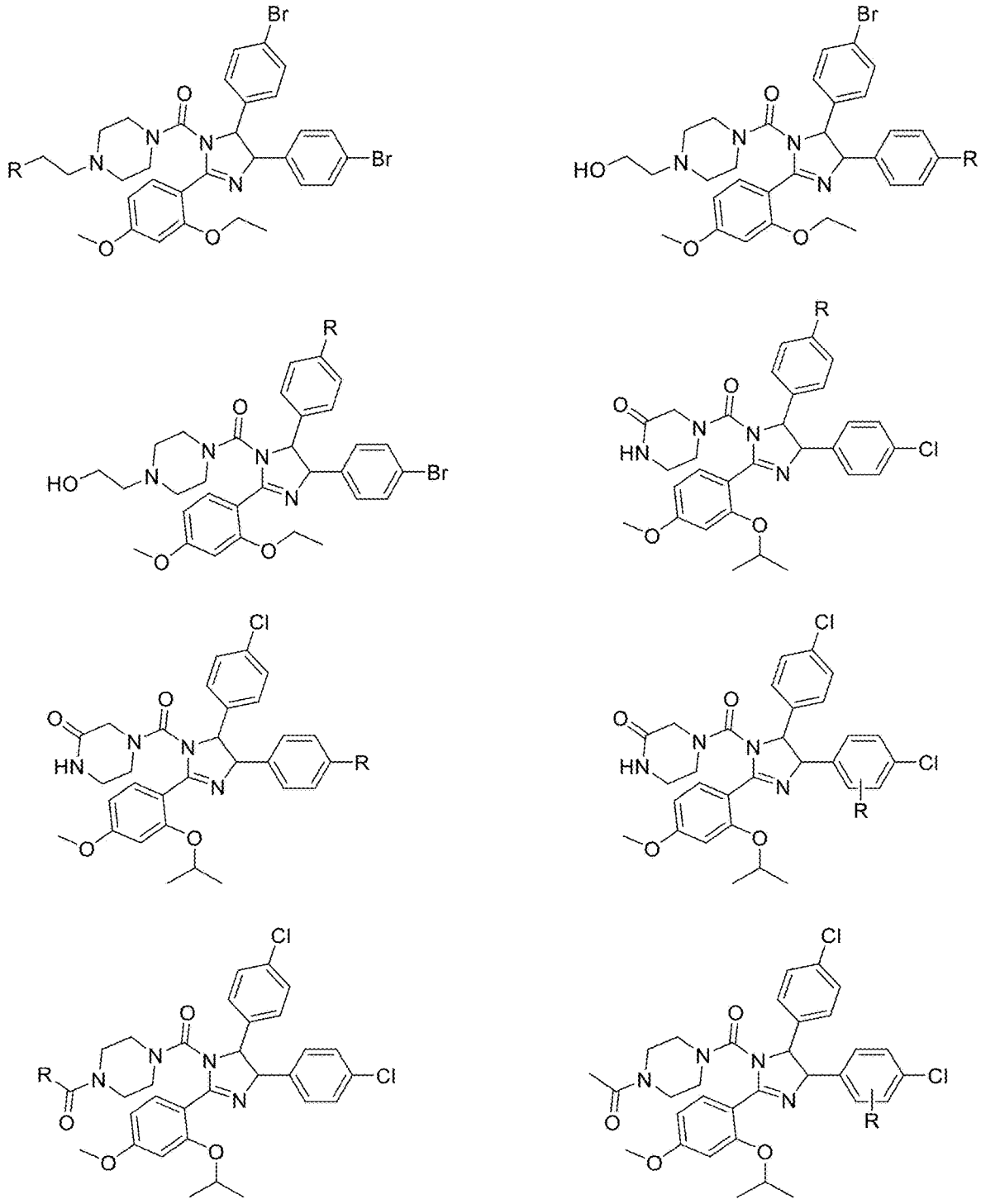


FIG. 1FF

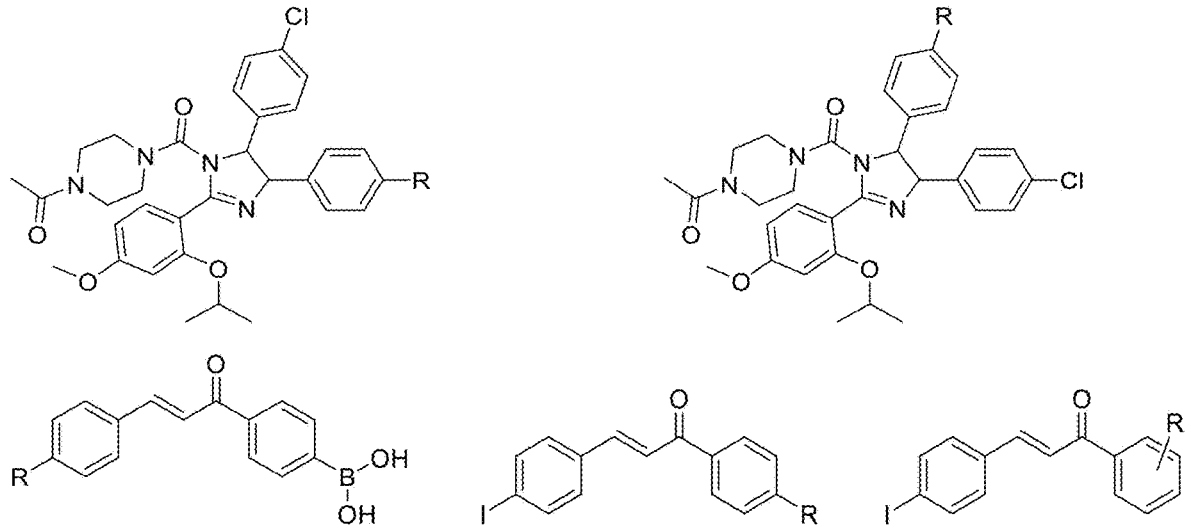


FIG. 1GG

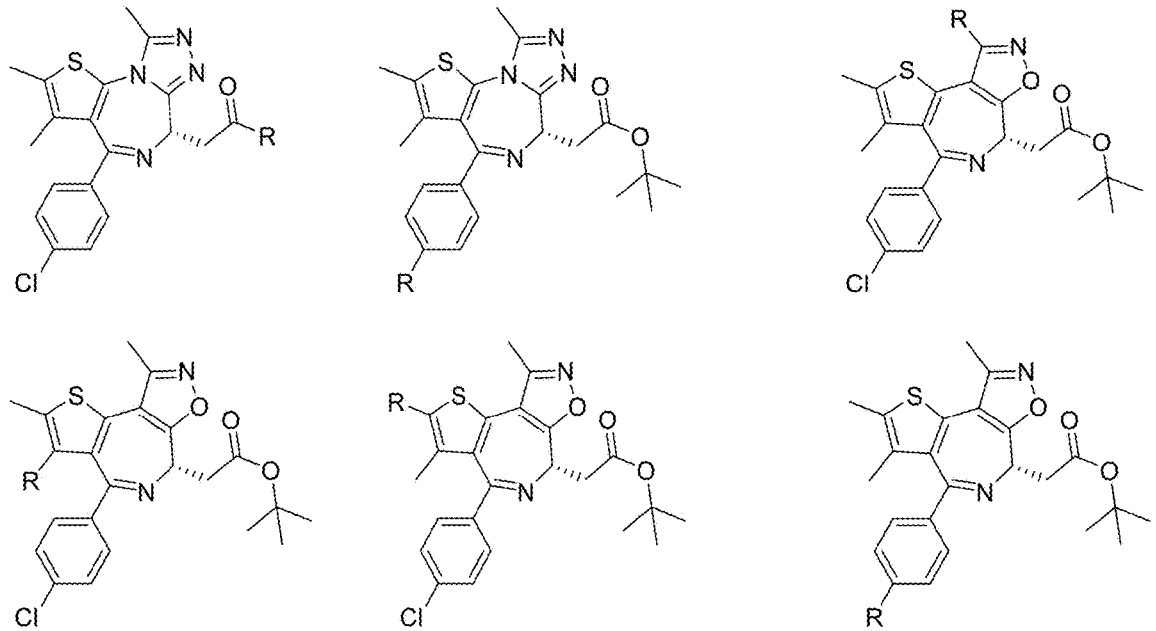


FIG. 1HH

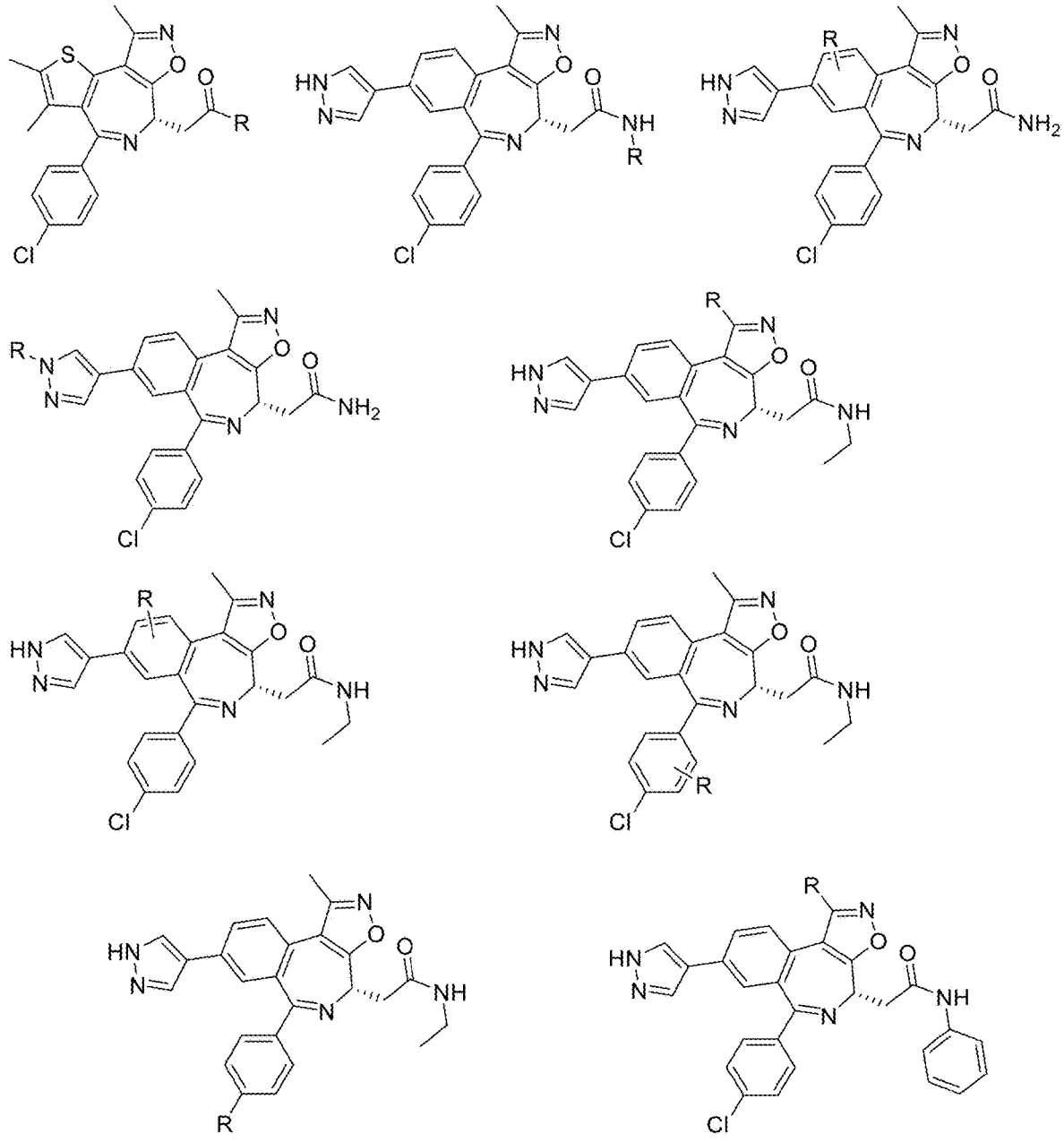


FIG. 1II

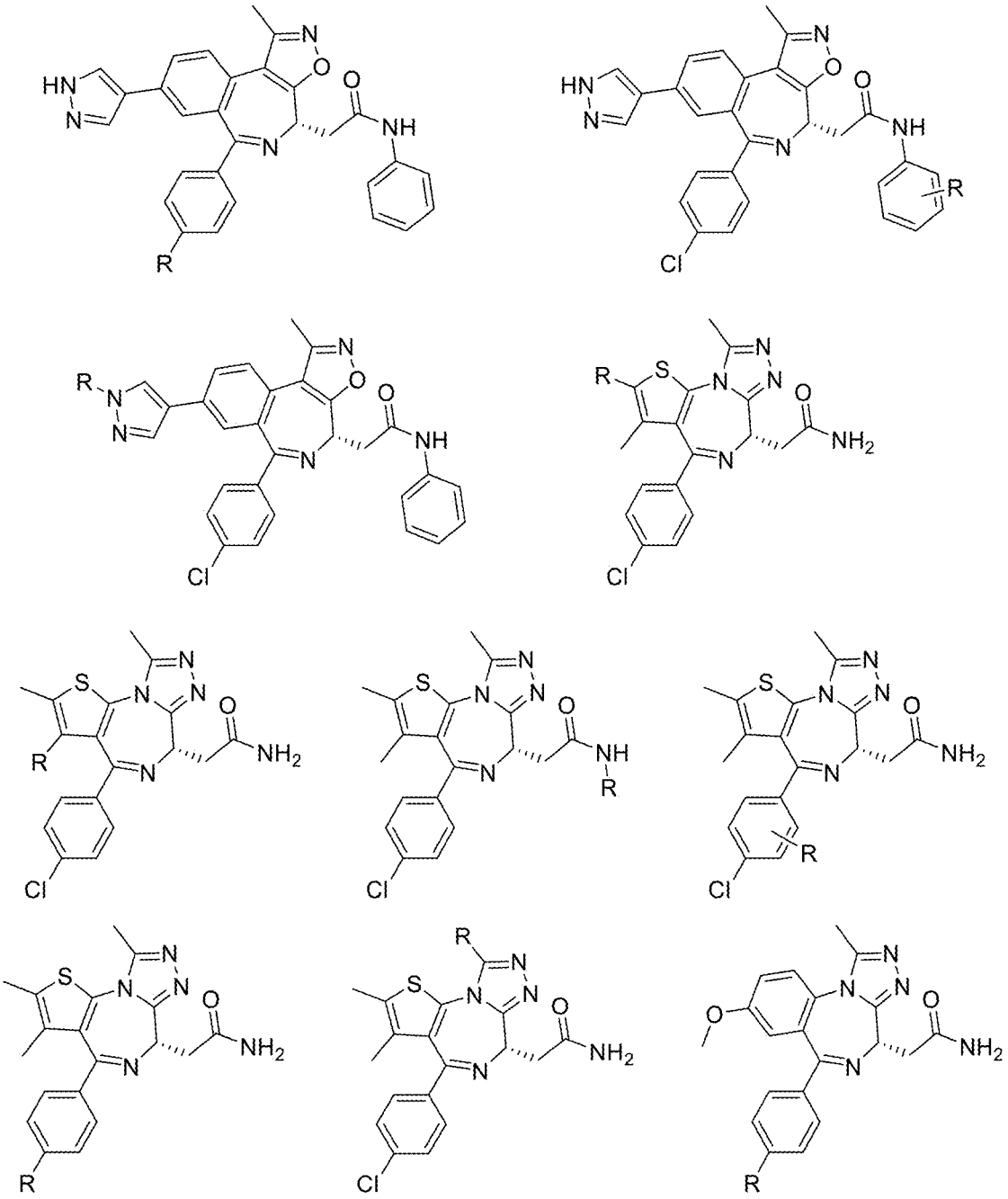


FIG. 1JJ

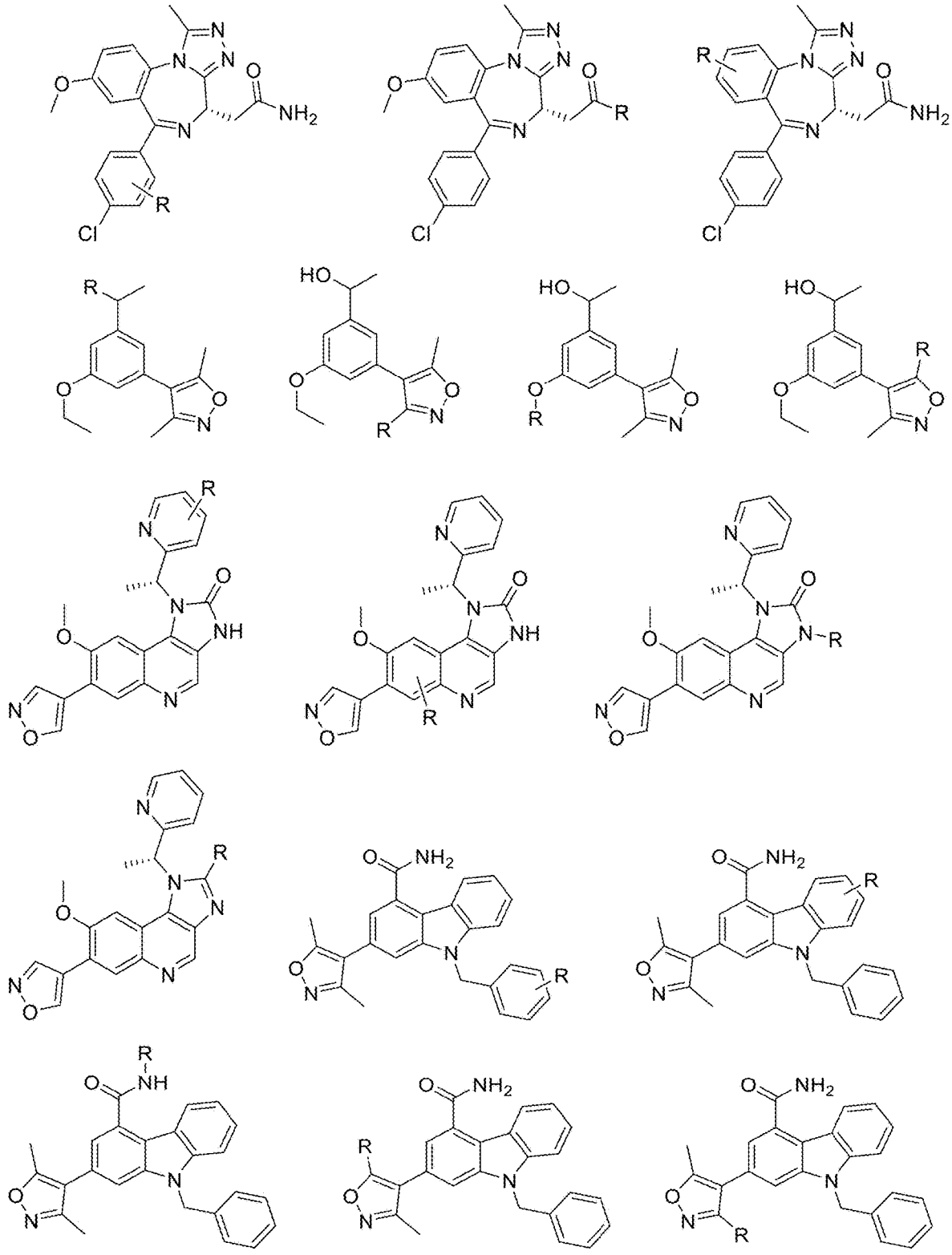


FIG. 1KK

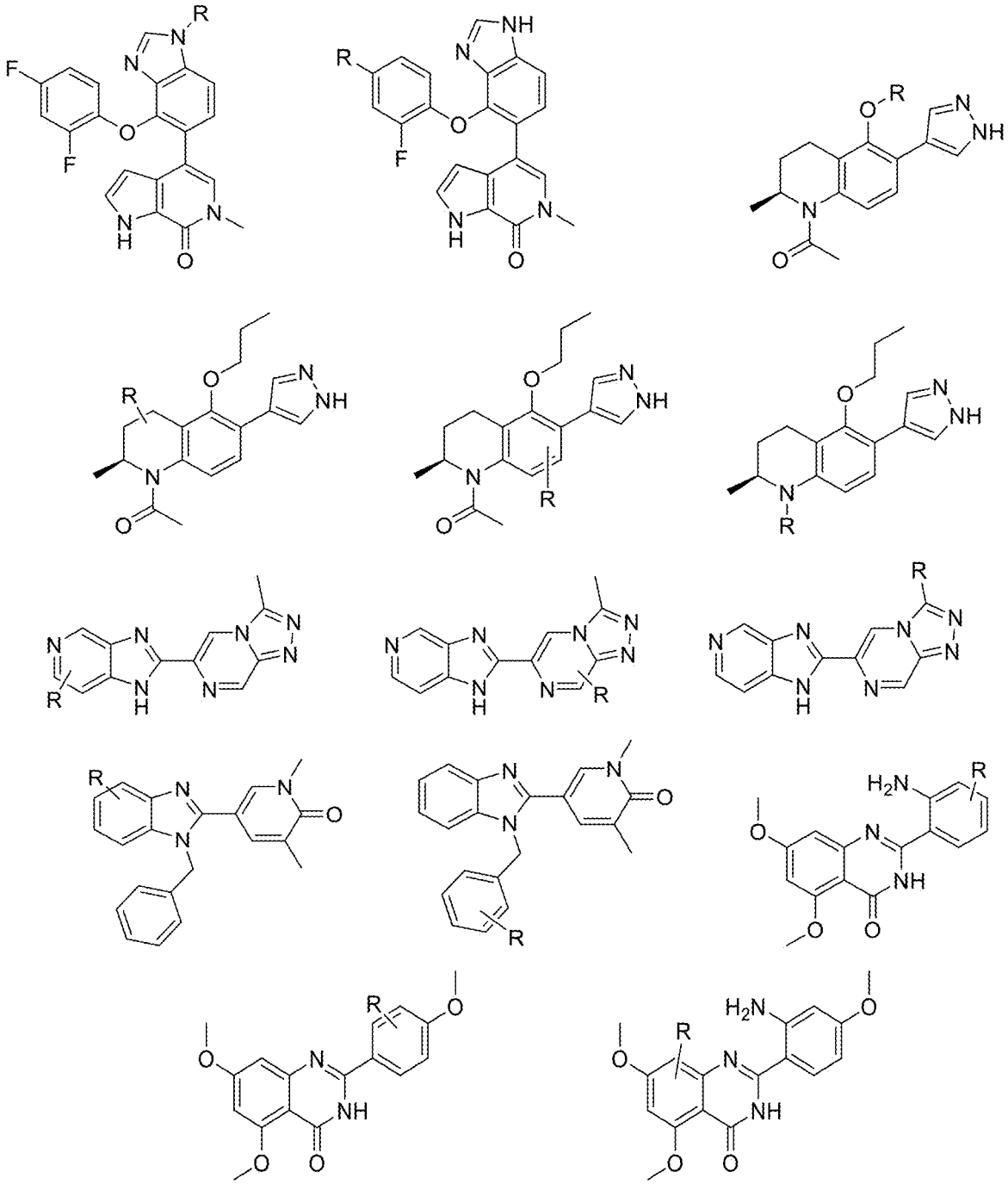


FIG. 1LL

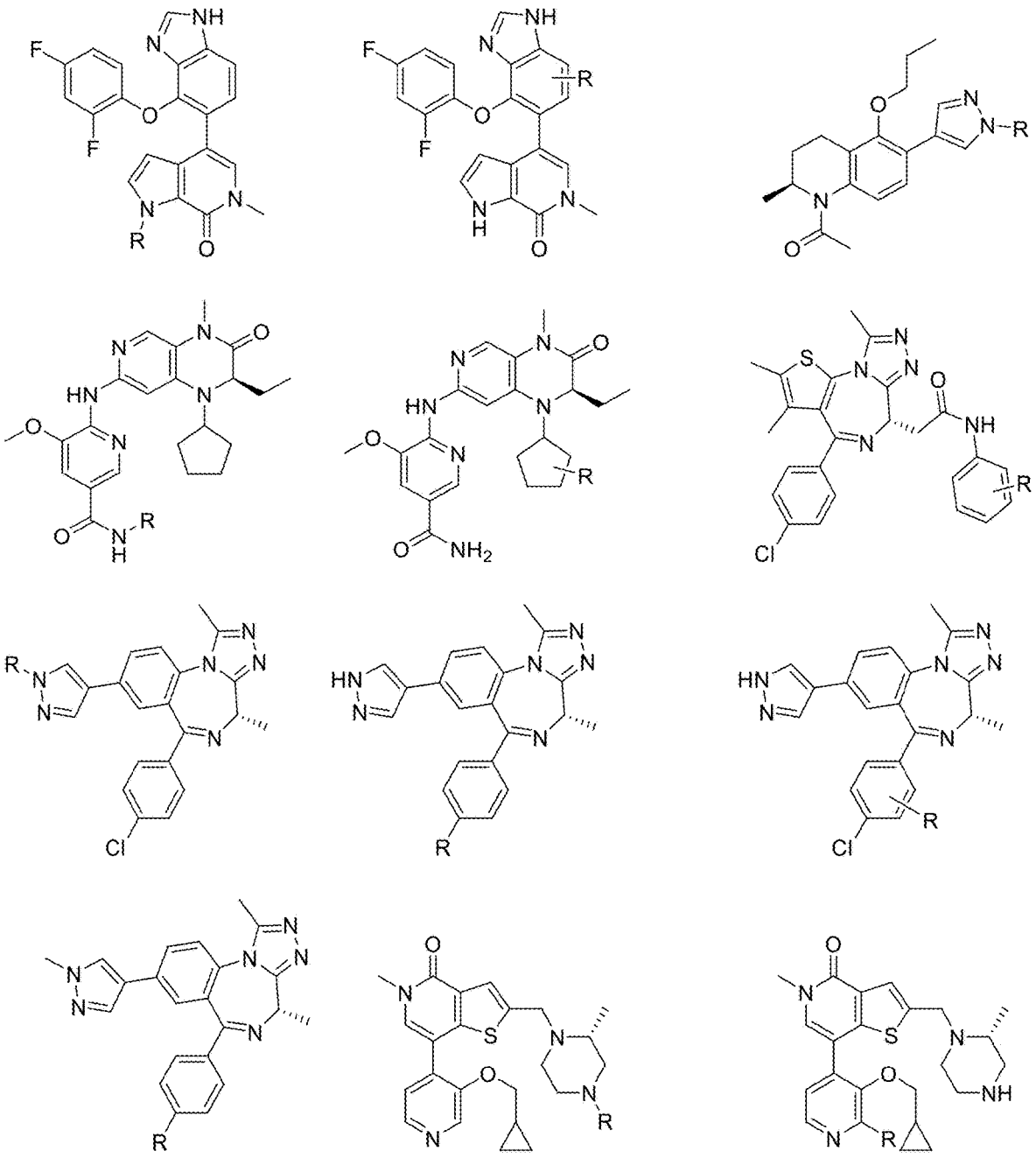


FIG. 1MM

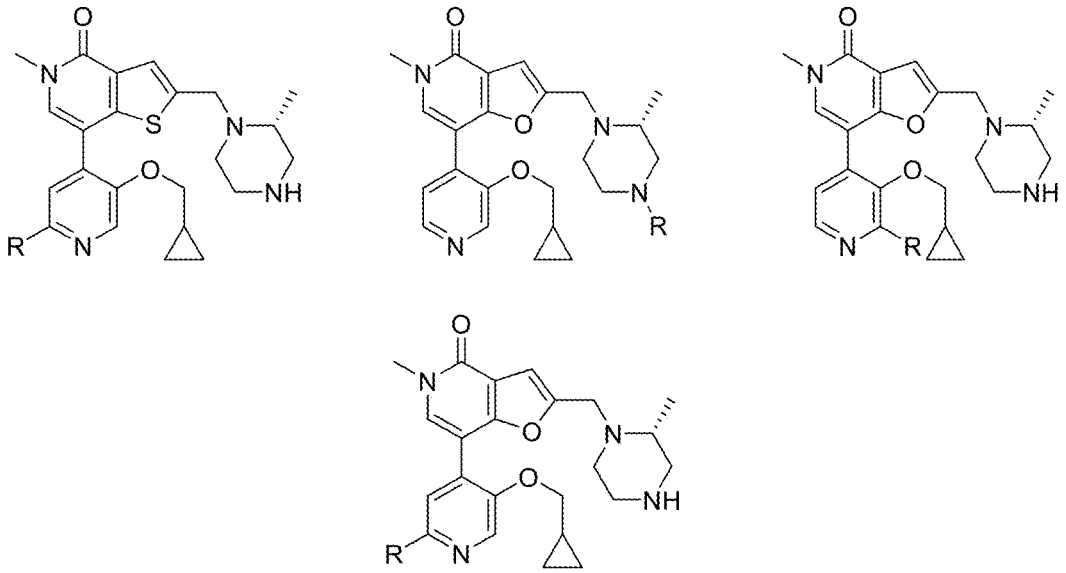


FIG. 1NN

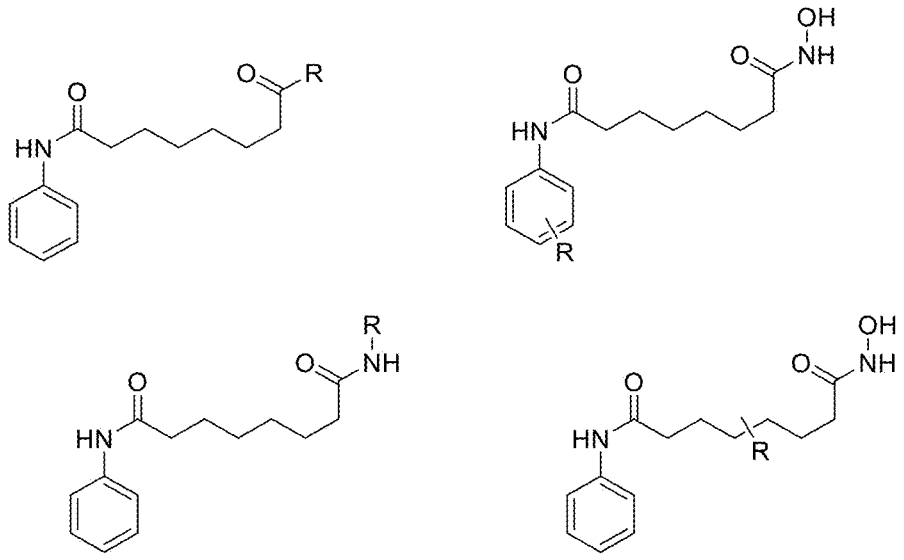


FIG. 1OO

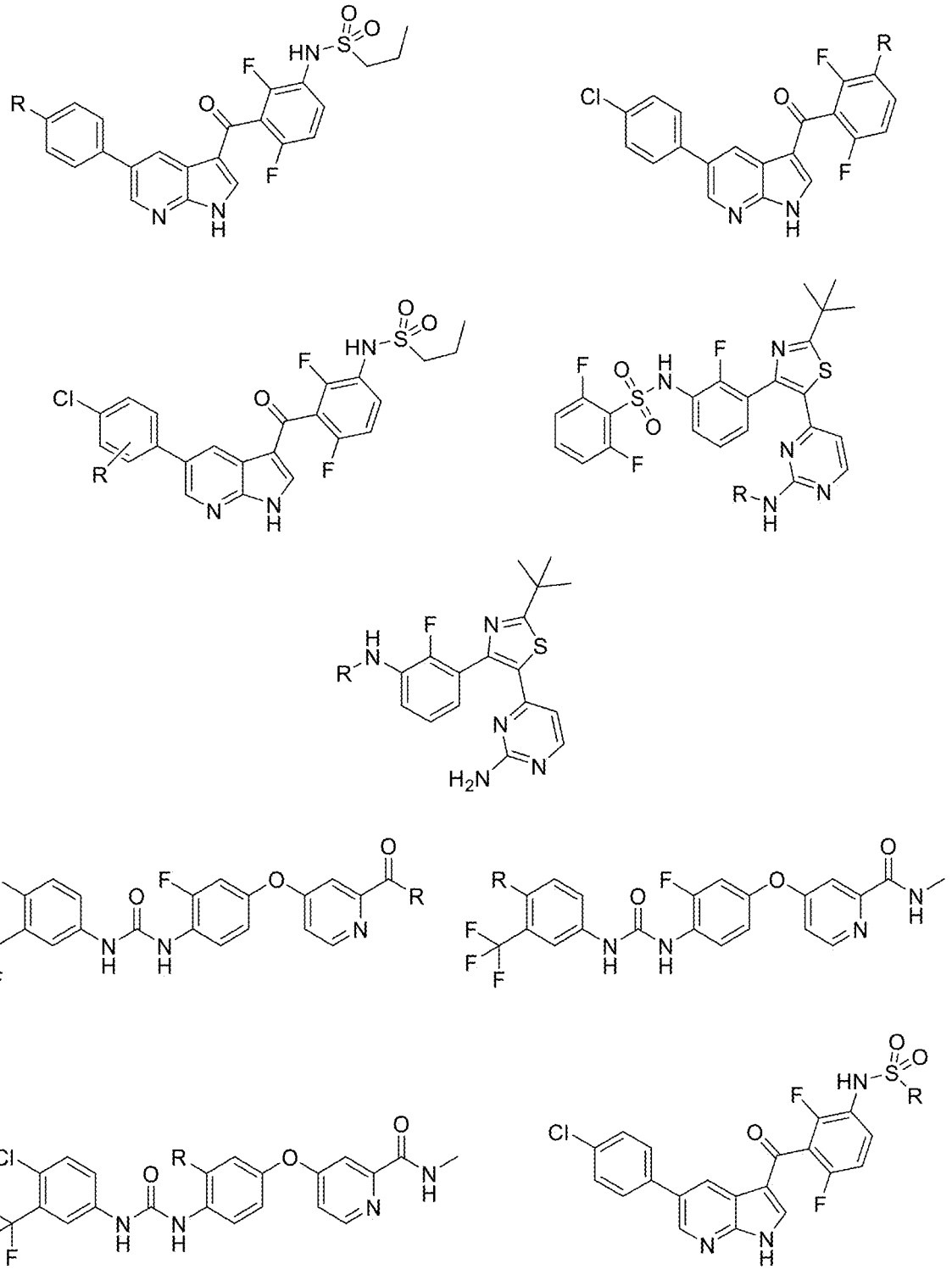


FIG. 1PP

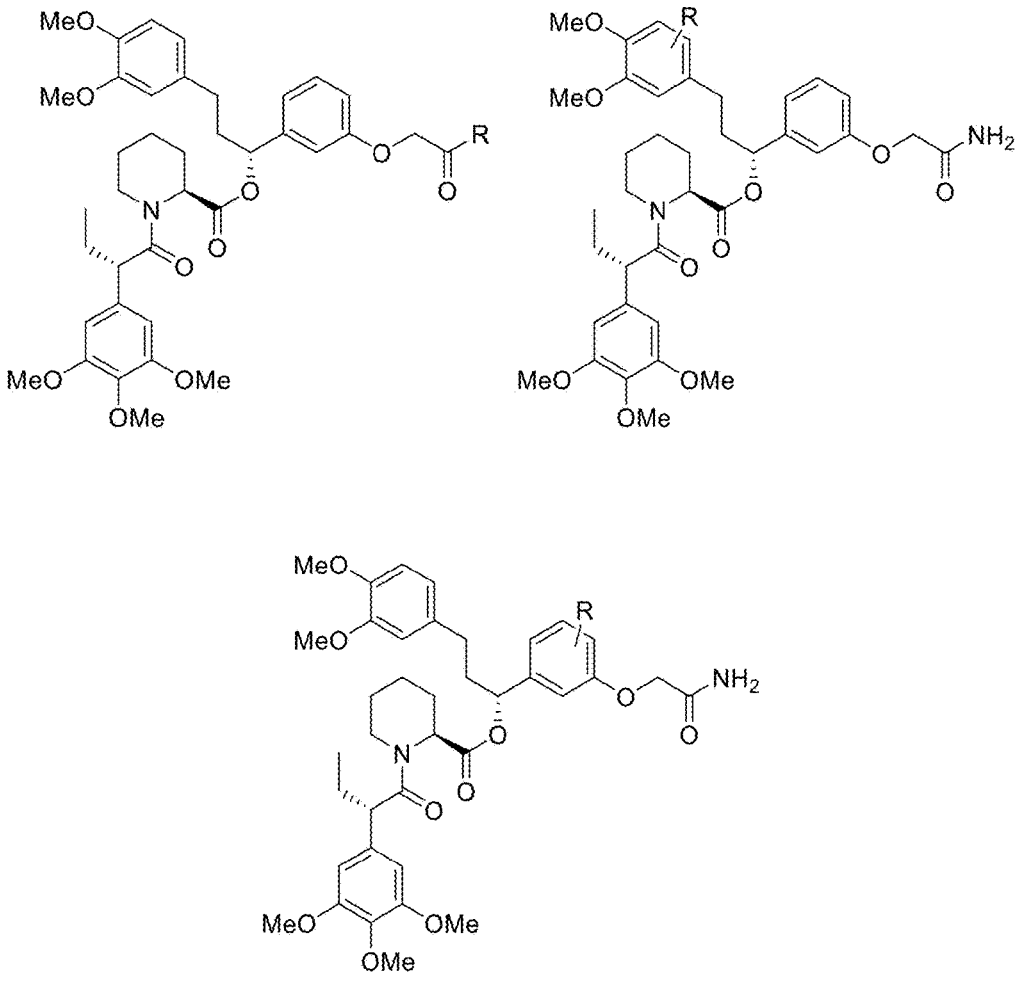


FIG. 1QQ

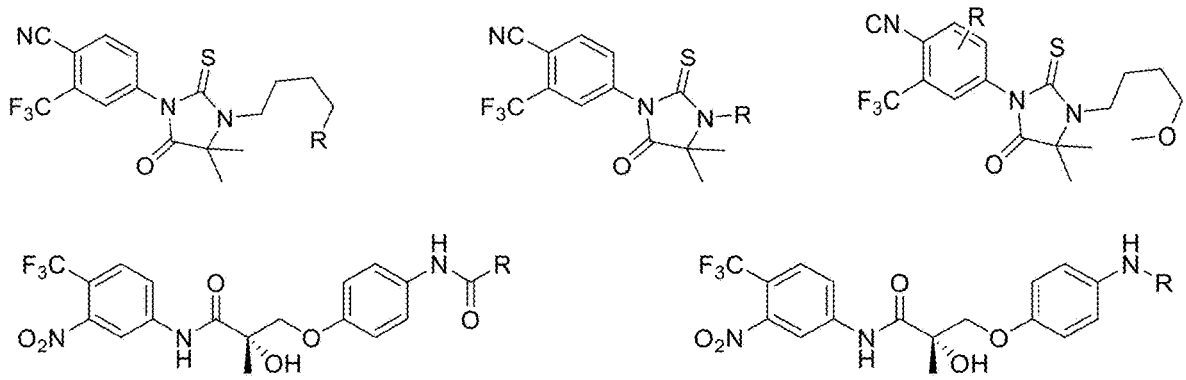


FIG. 1RR

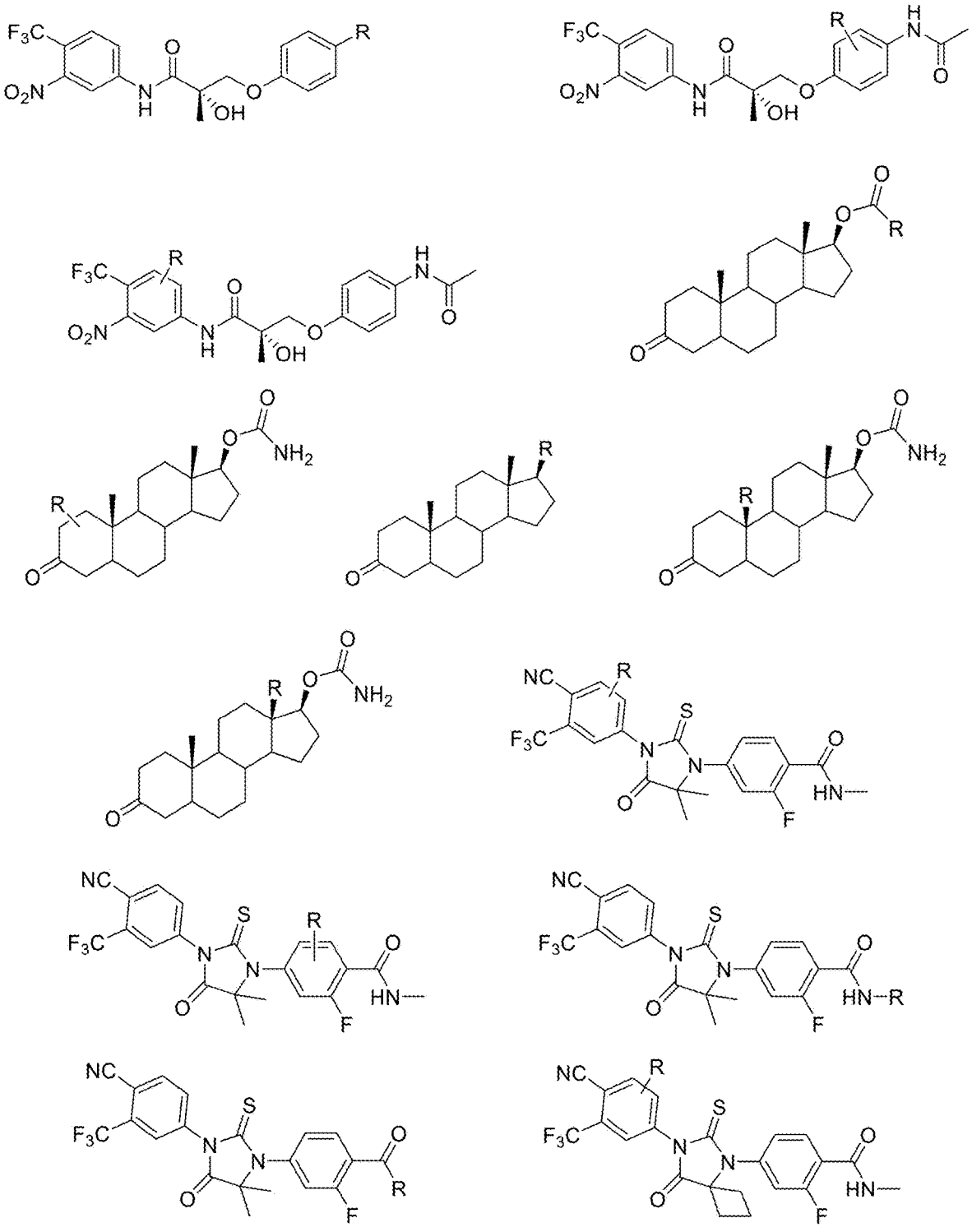


FIG. 1SS

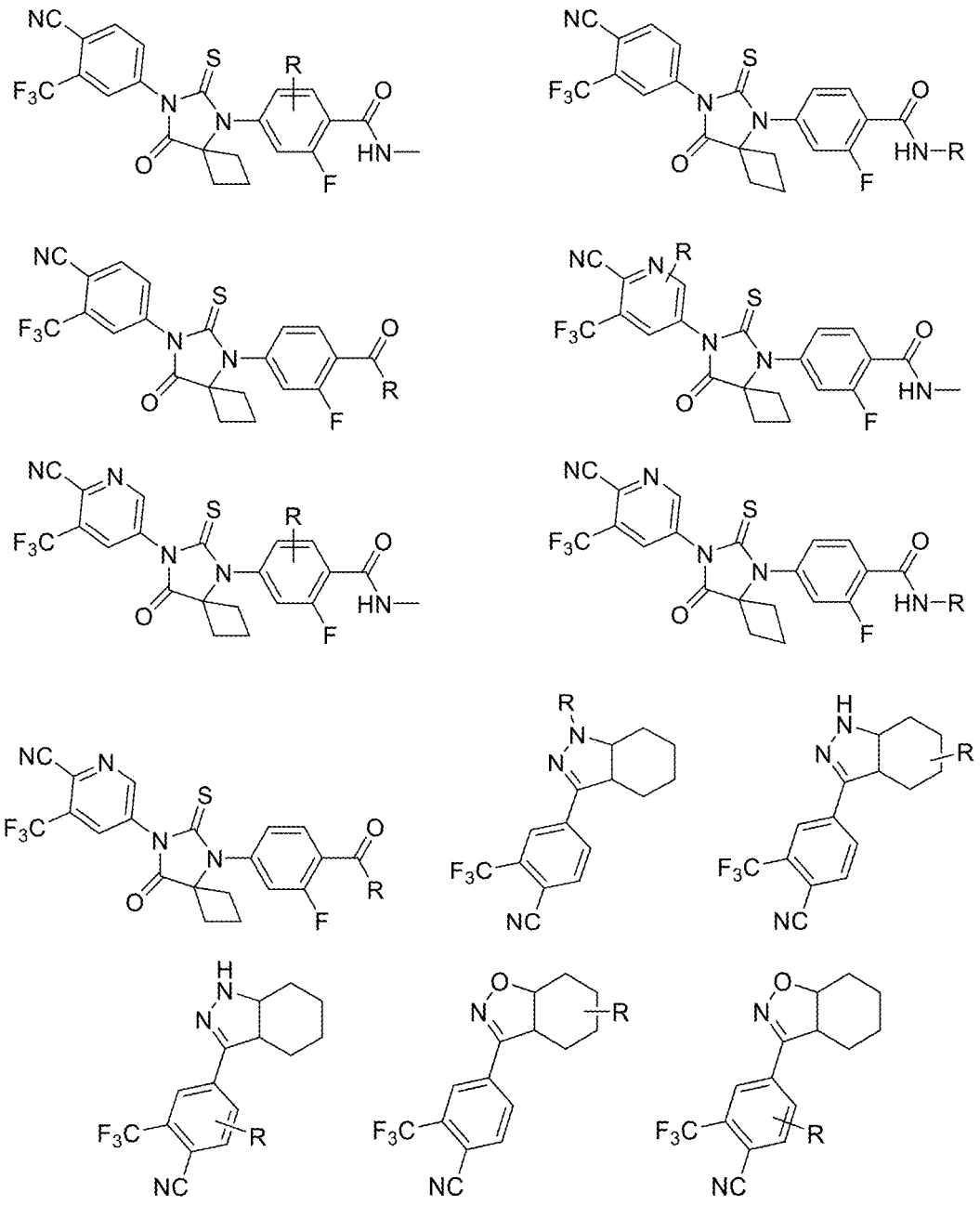
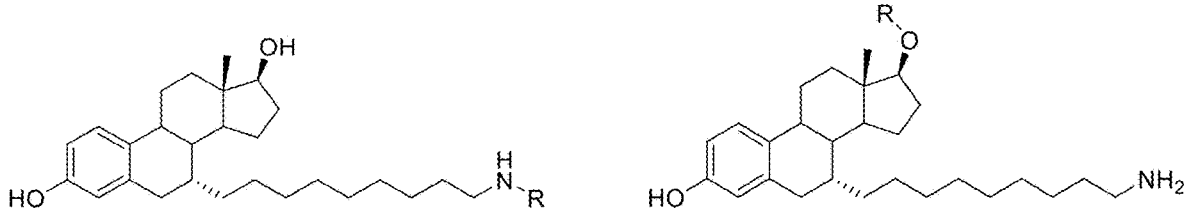


FIG. 1TT

FIG. 1UU



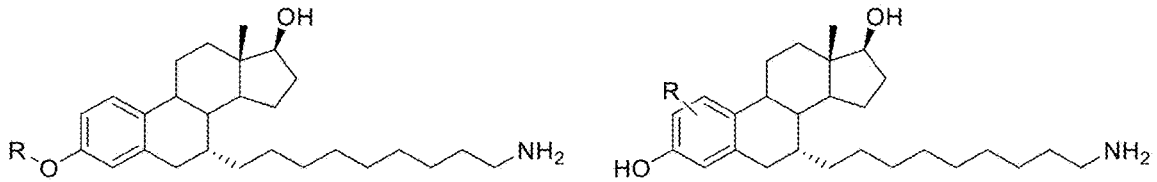


FIG. 1VV

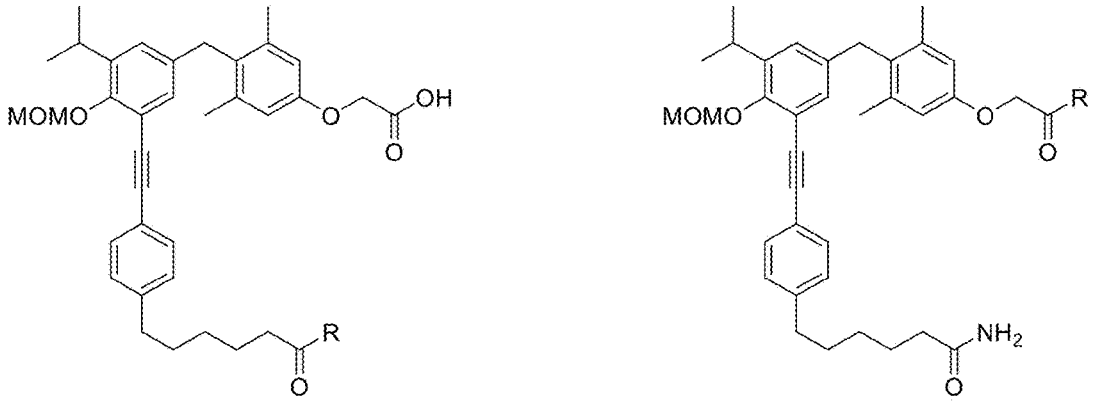


FIG. 1WW

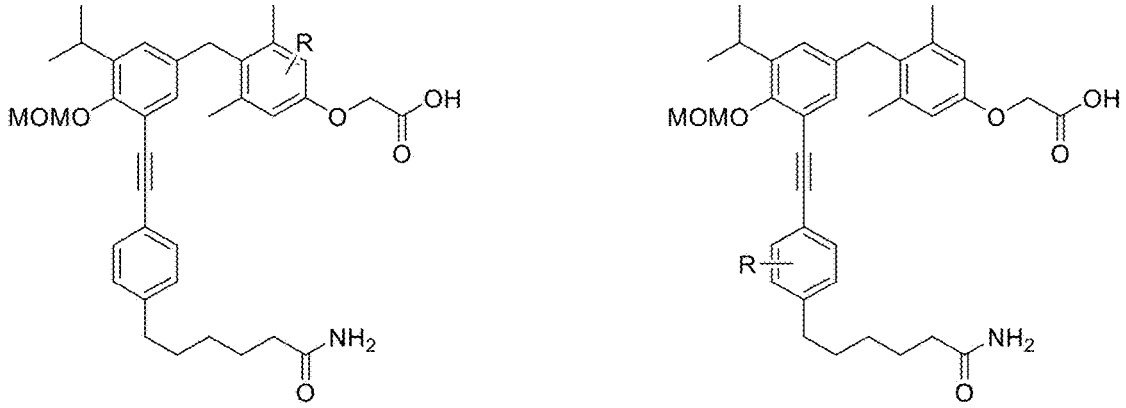


FIG. 1XX

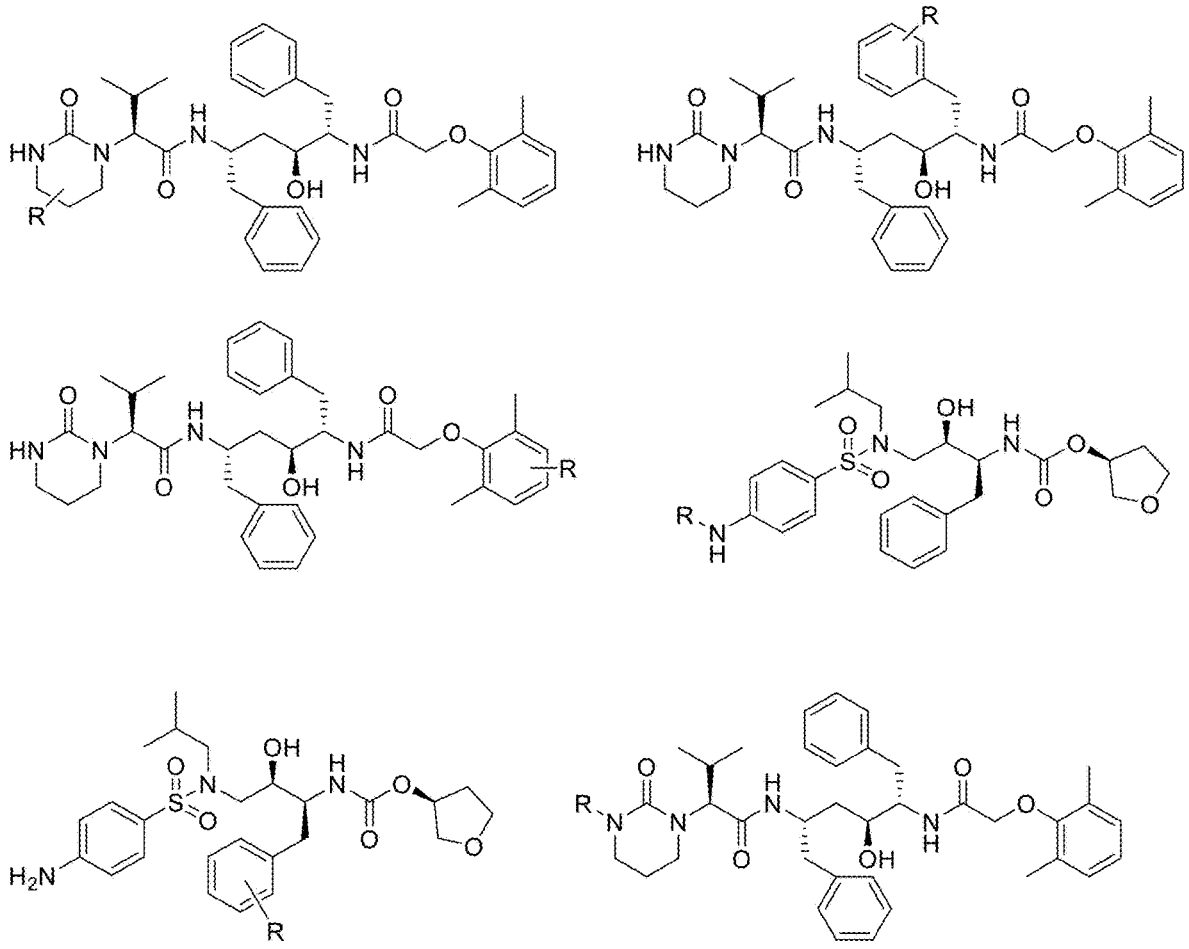


FIG. 1YY

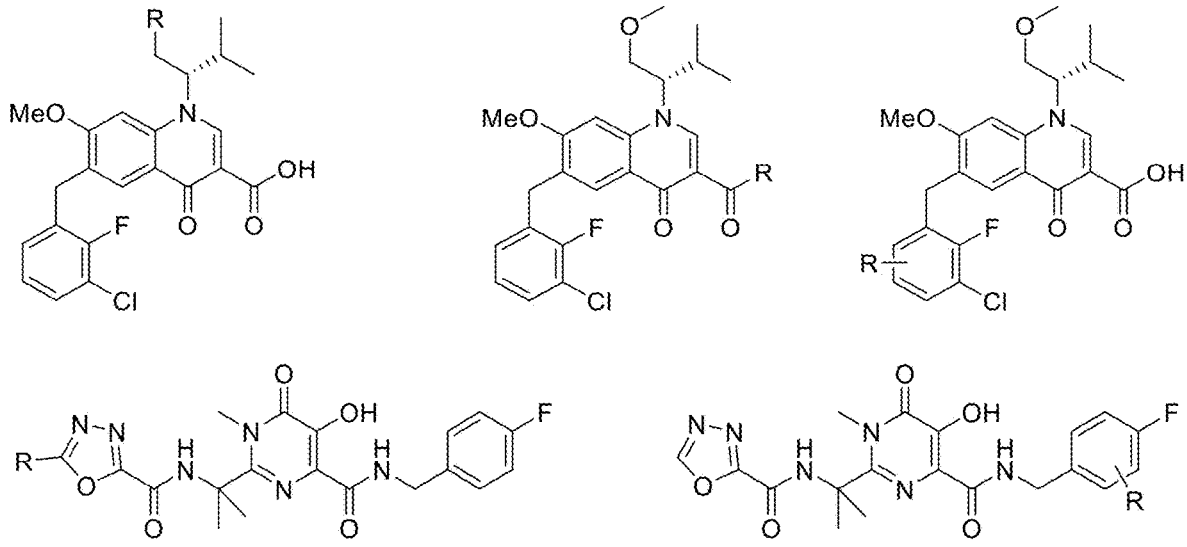


FIG. 1ZZ

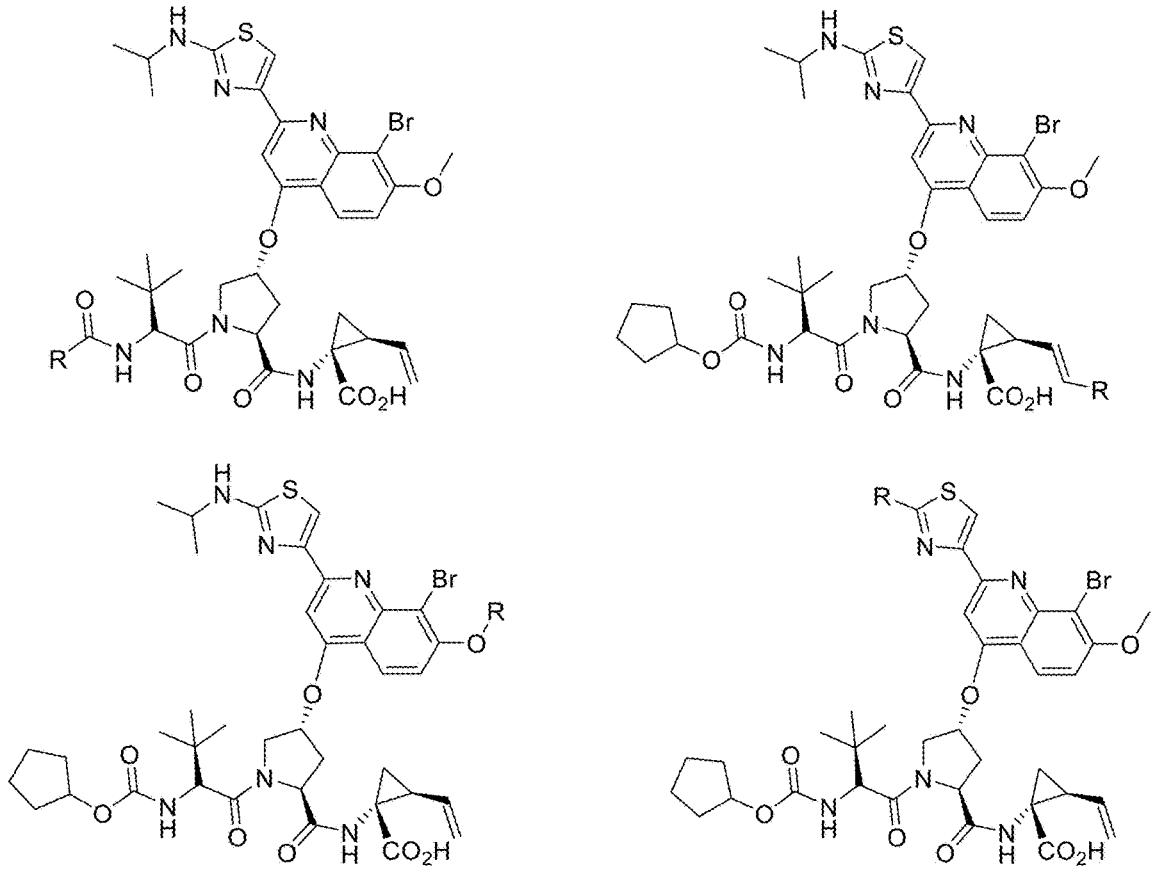


FIG. 1AAA

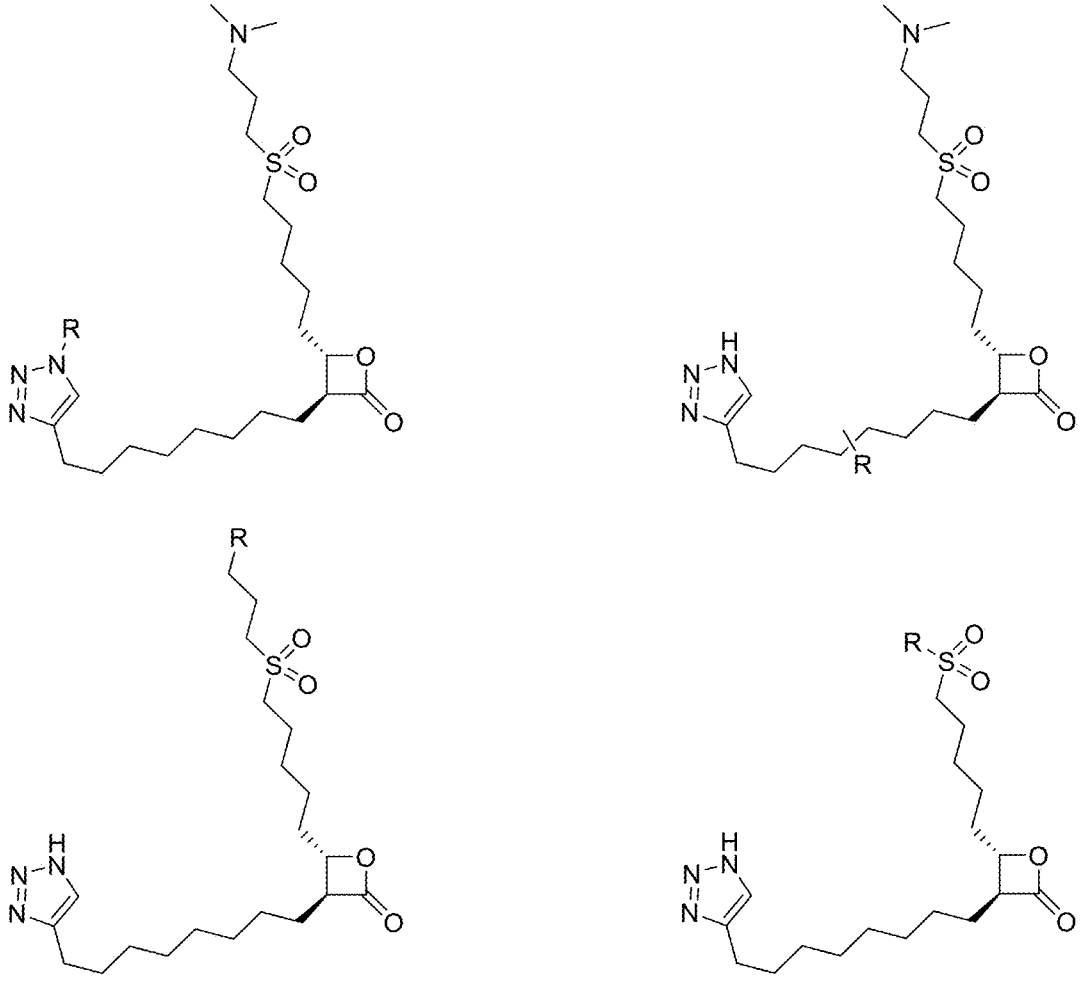


FIG. 1BBB

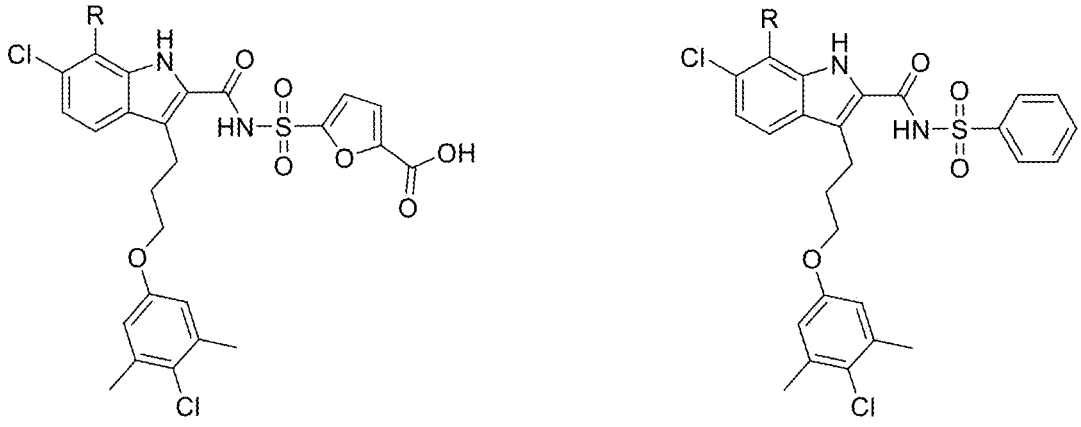


FIG. 1CCC

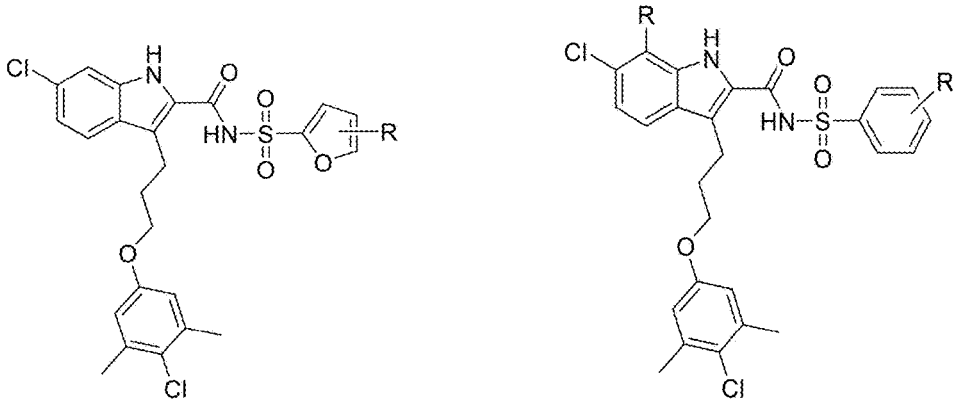


FIG. 1DDD

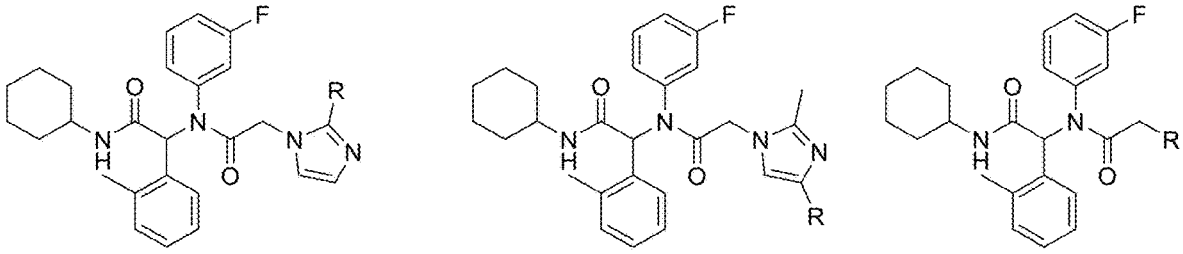


FIG. 1EEE

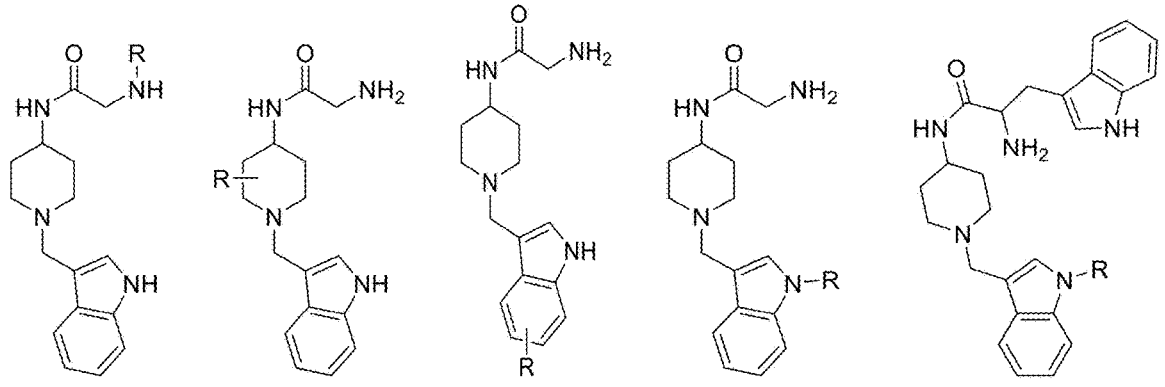


FIG. 1FFF

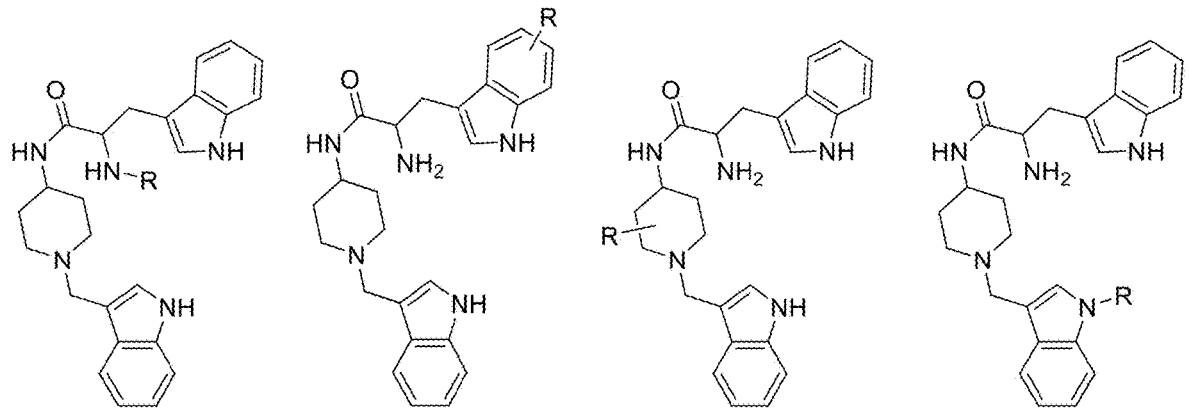


FIG. 1GGG

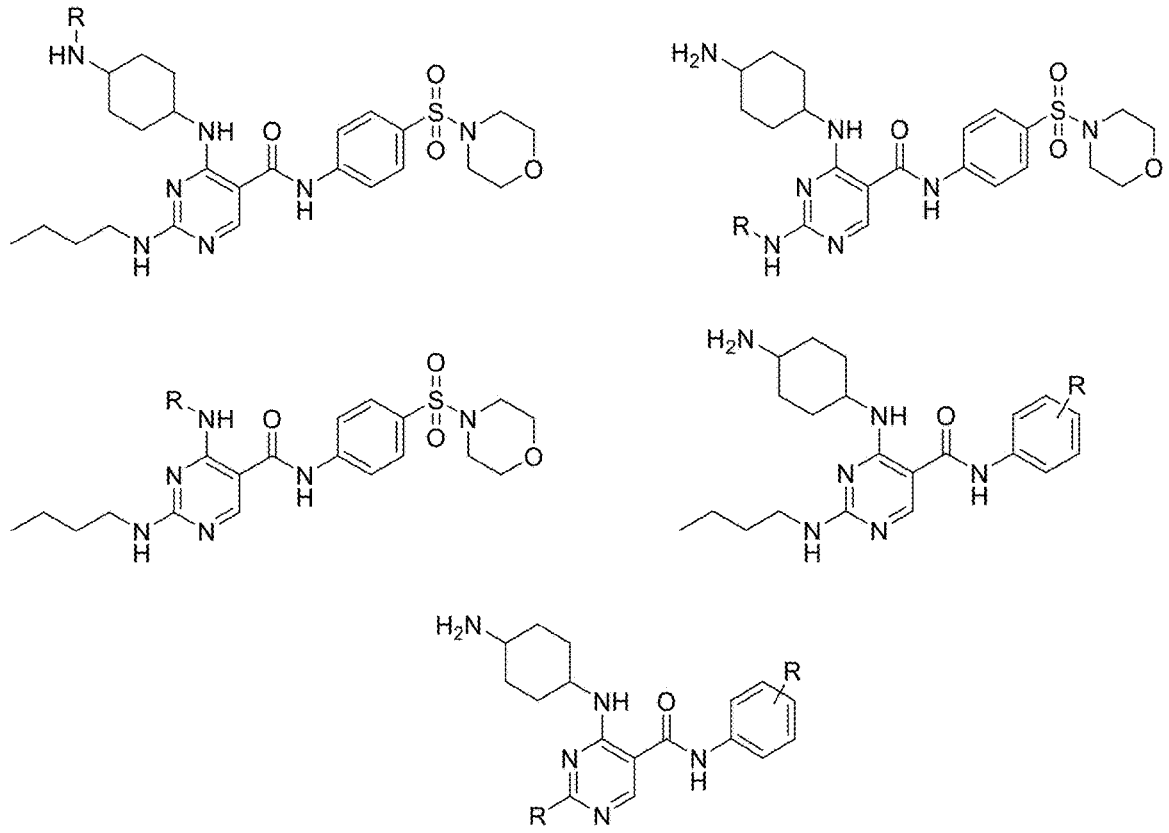
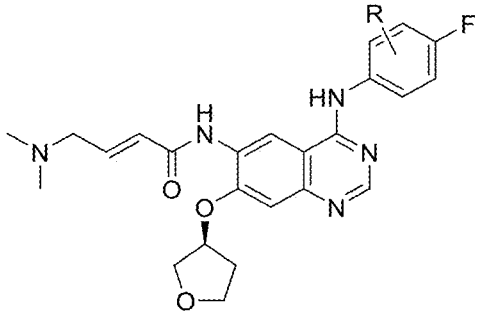
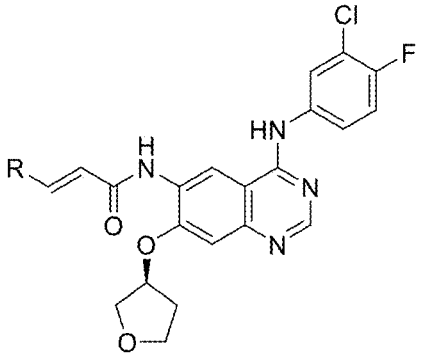
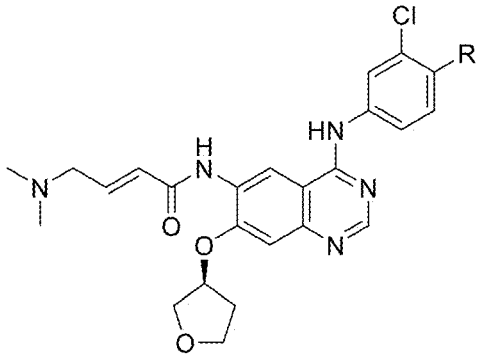
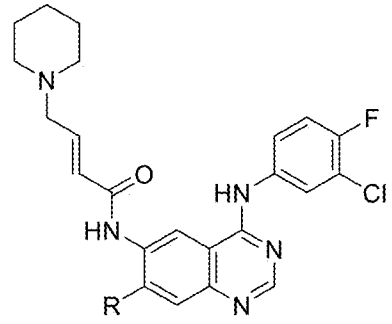


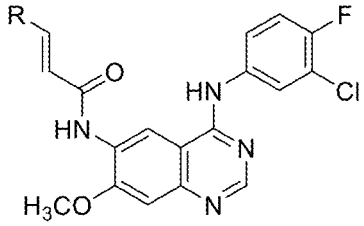
FIG. 1HHH

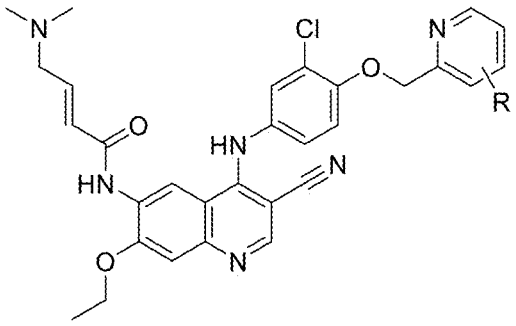


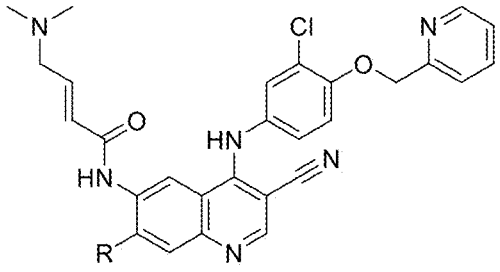












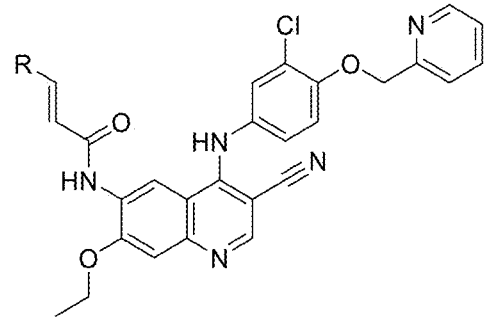


FIG. 1III

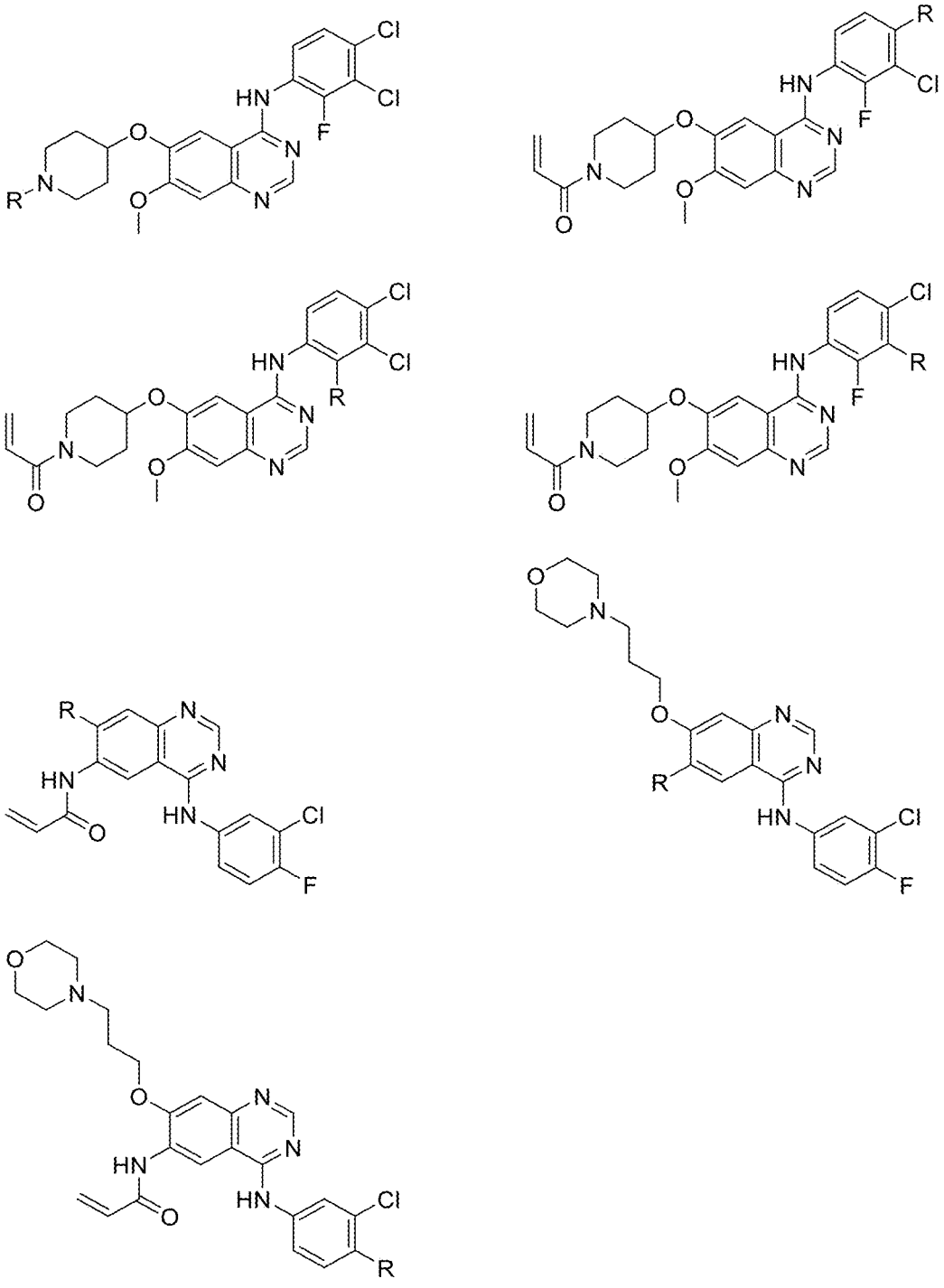


FIG. 1JJJ

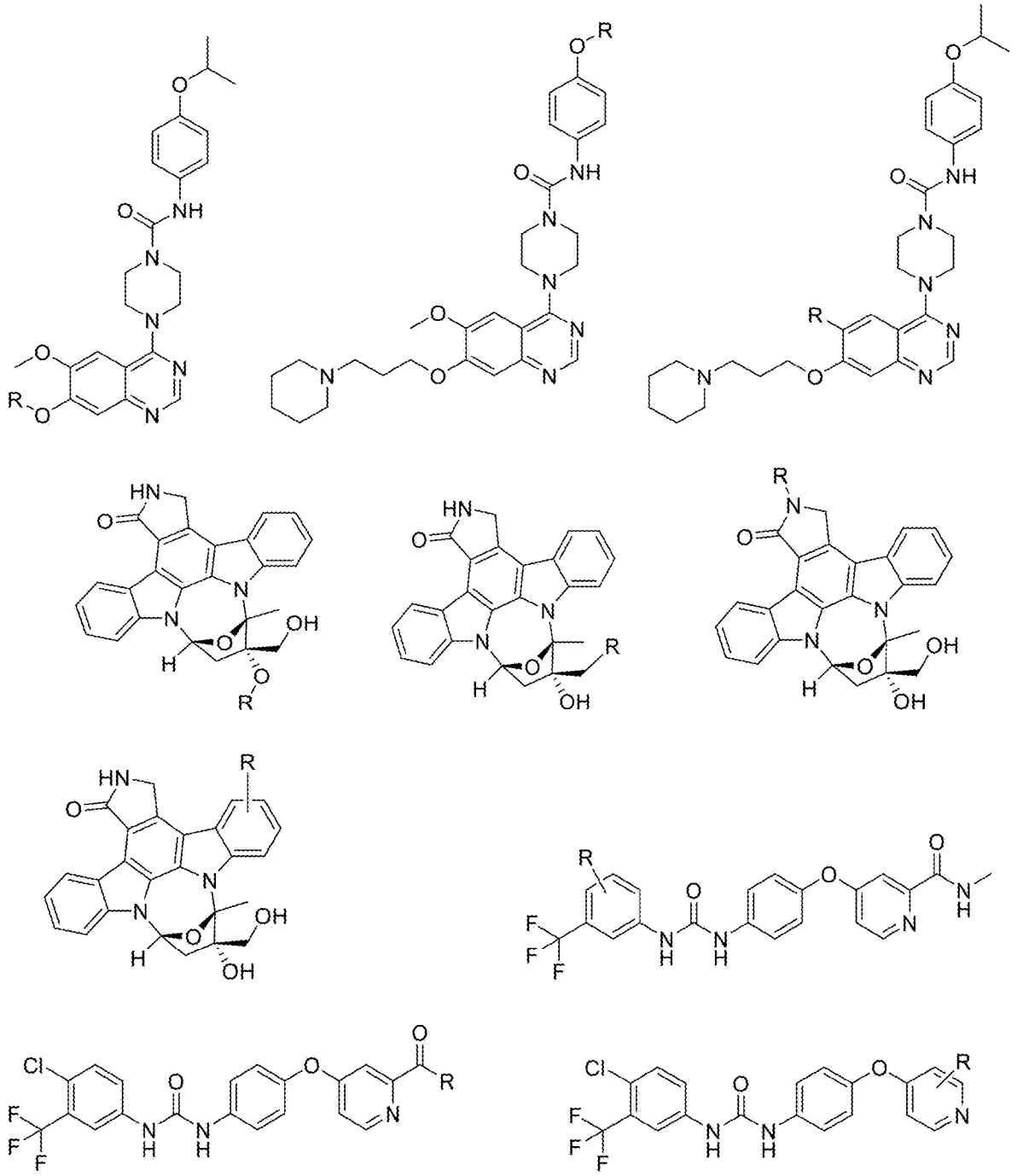


FIG. 1KKK

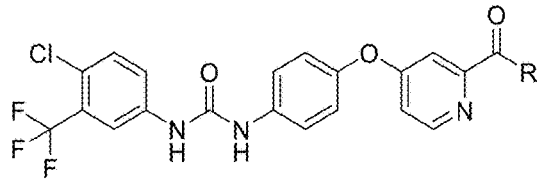
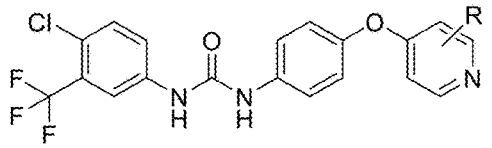
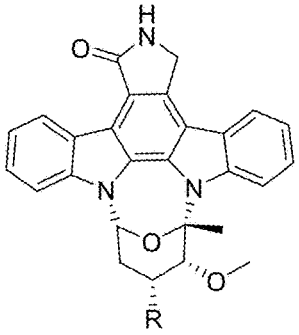
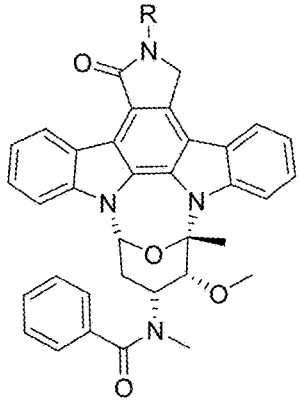
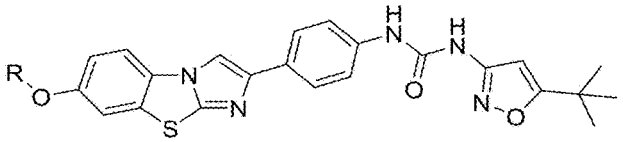
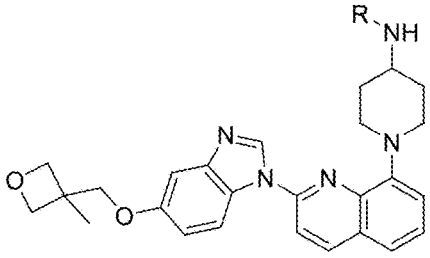
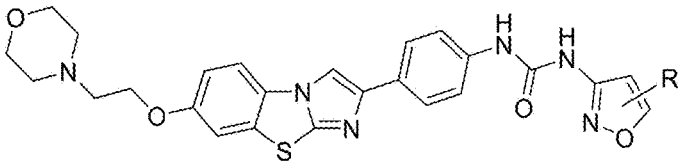
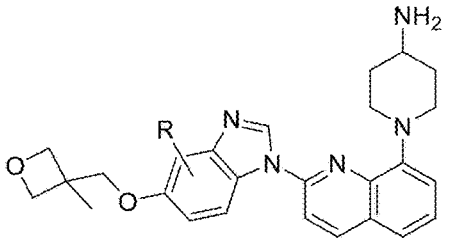
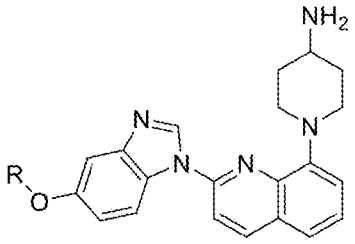










FIG. 1LLL

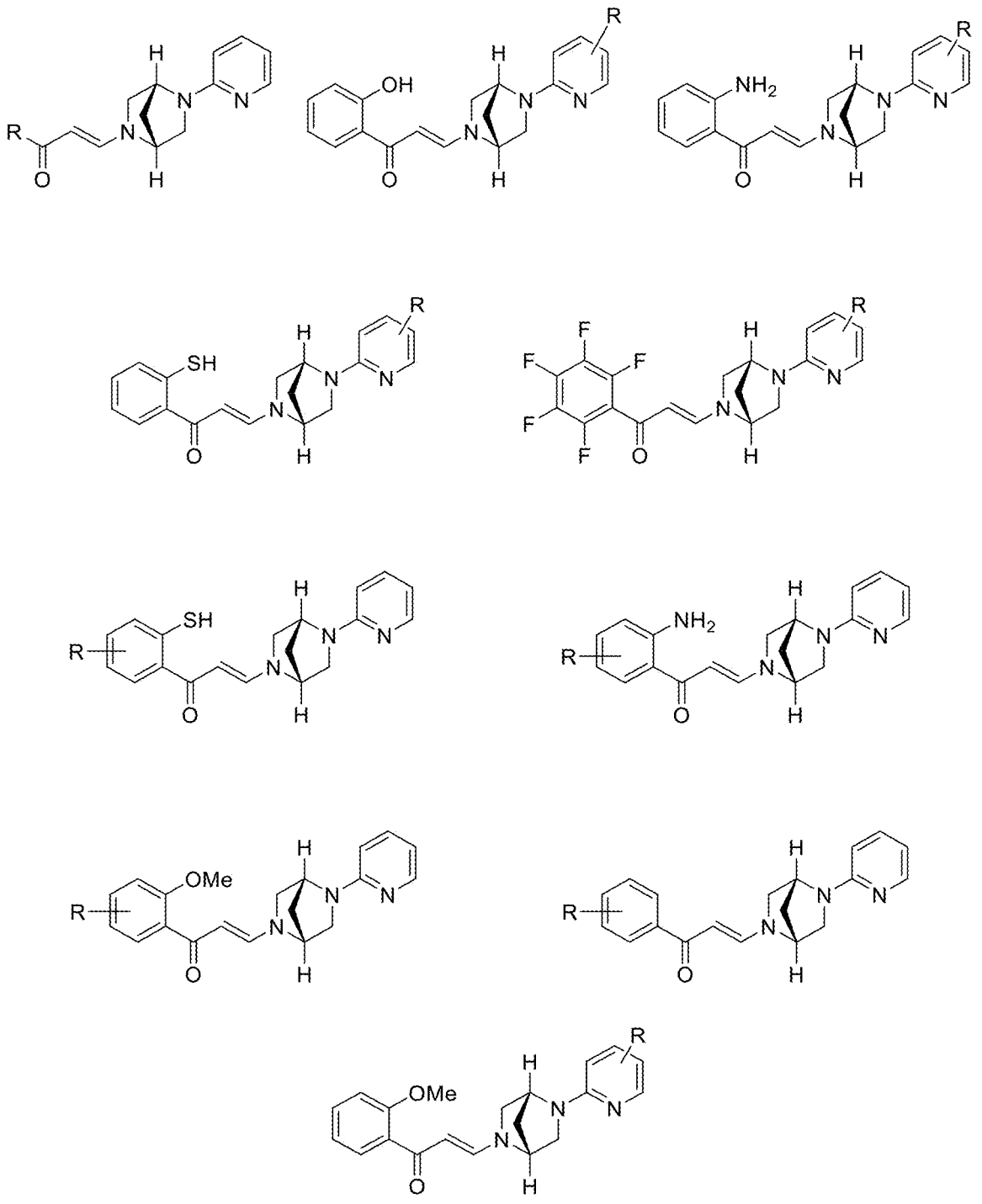


FIG. 2A

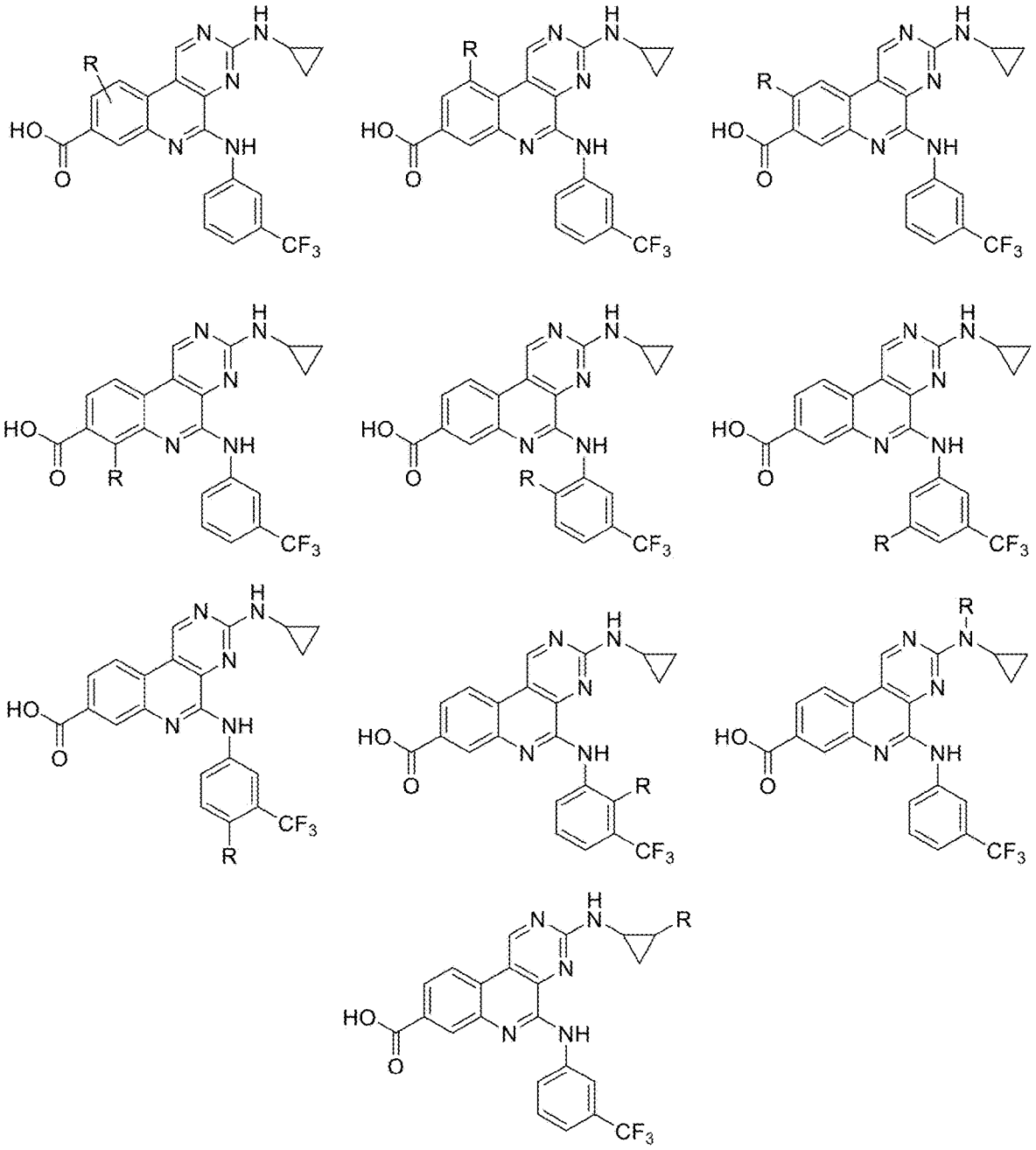


FIG. 2B

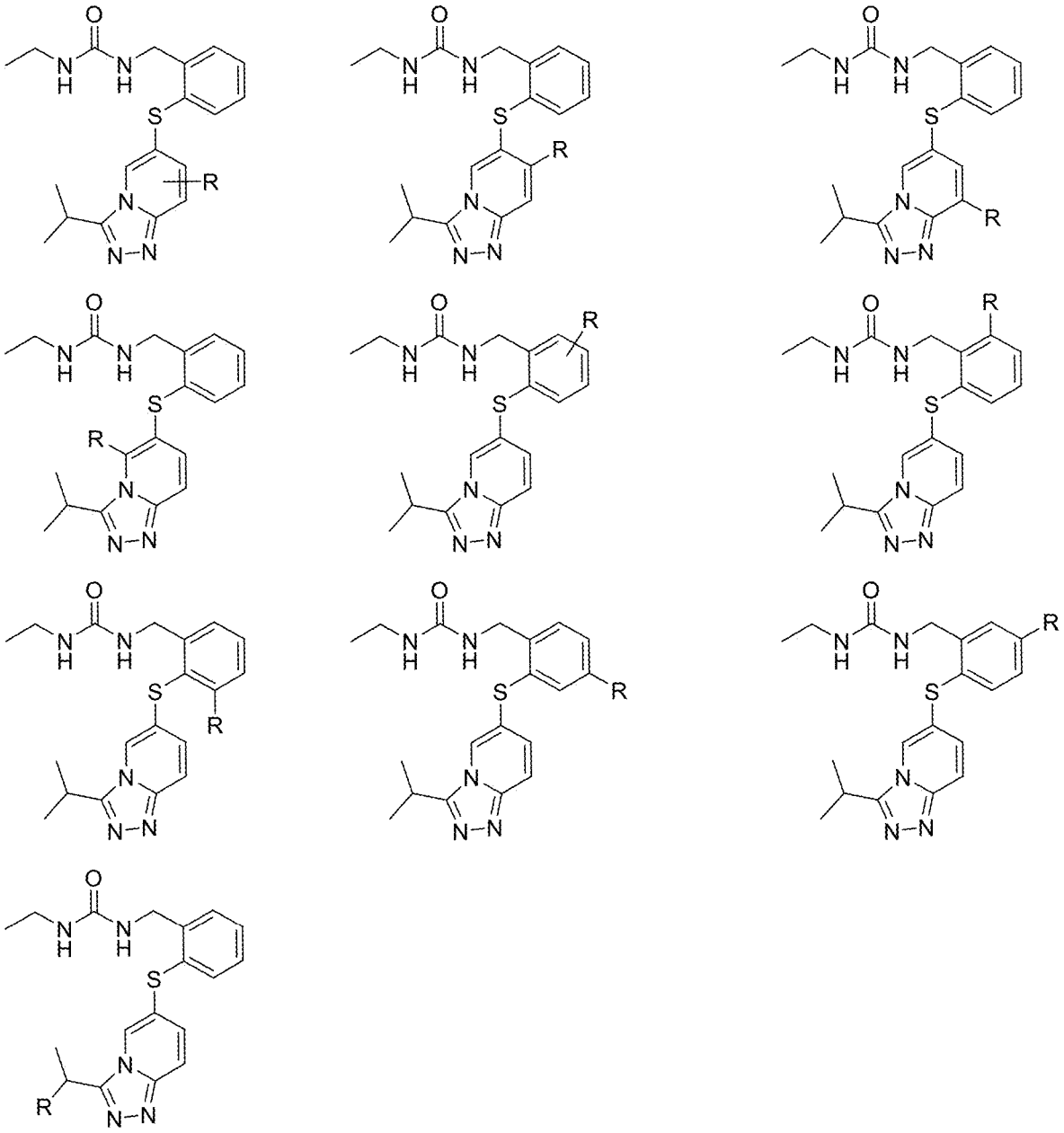


FIG. 2C

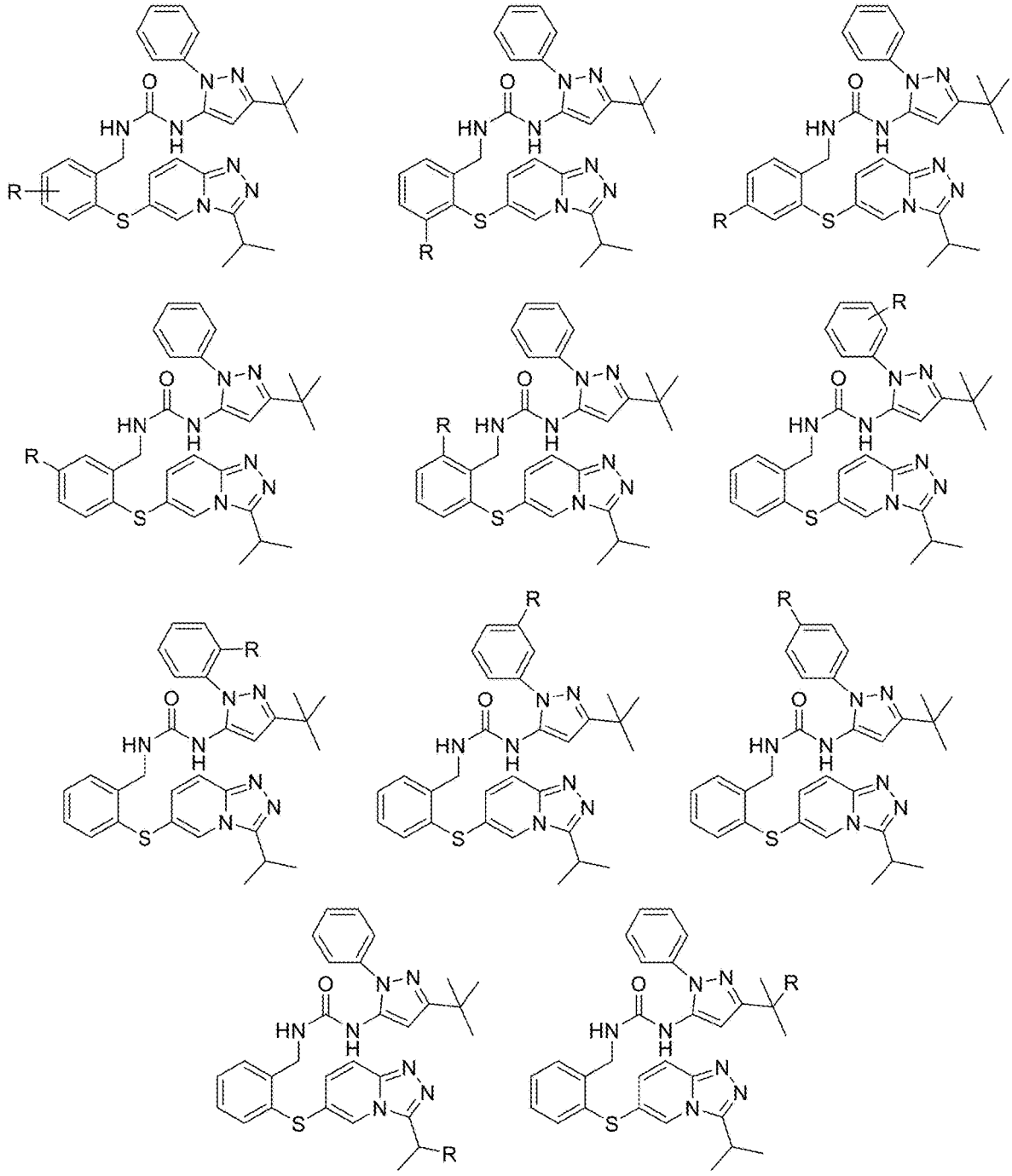


FIG. 2D

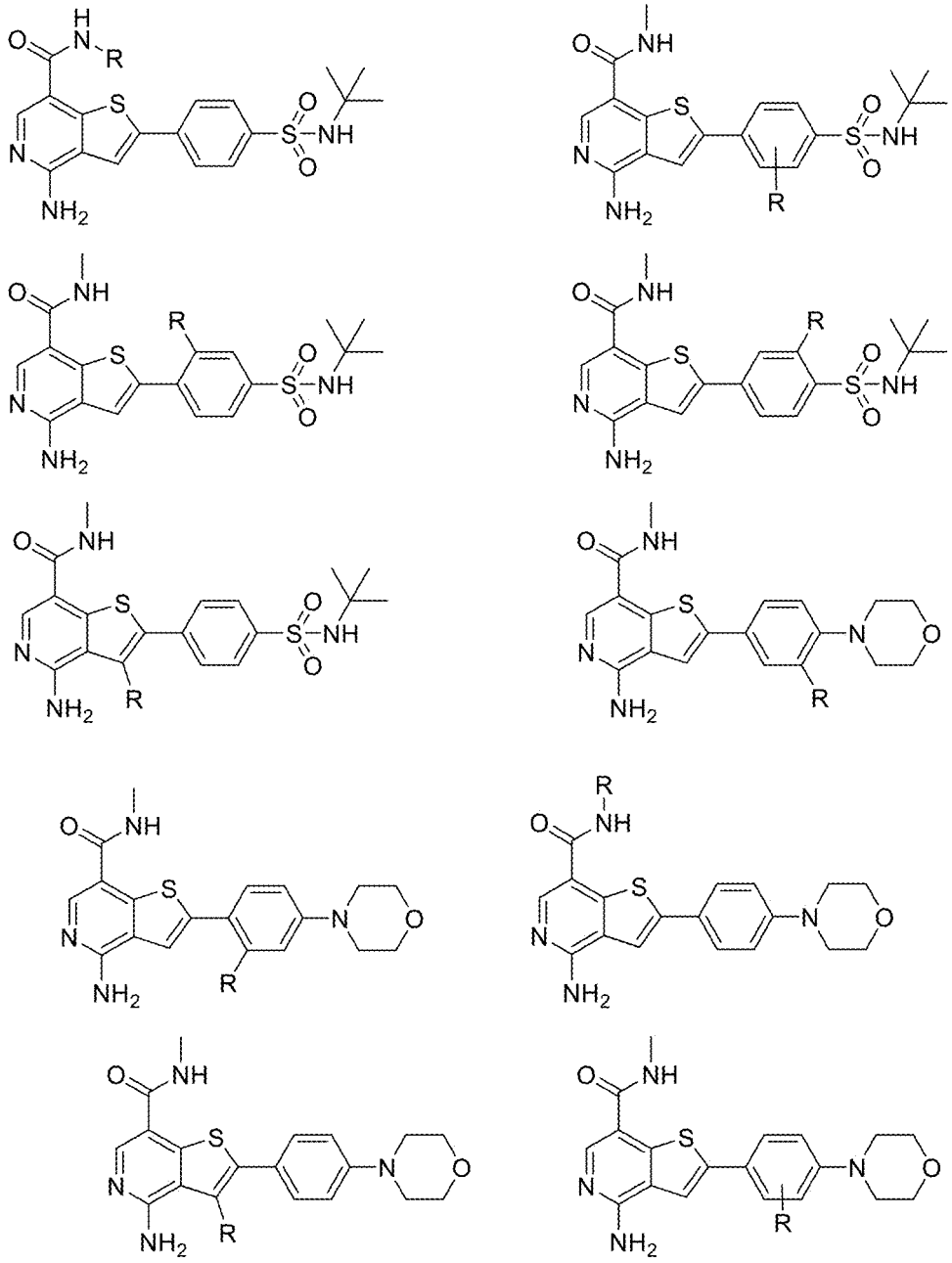


FIG. 2E

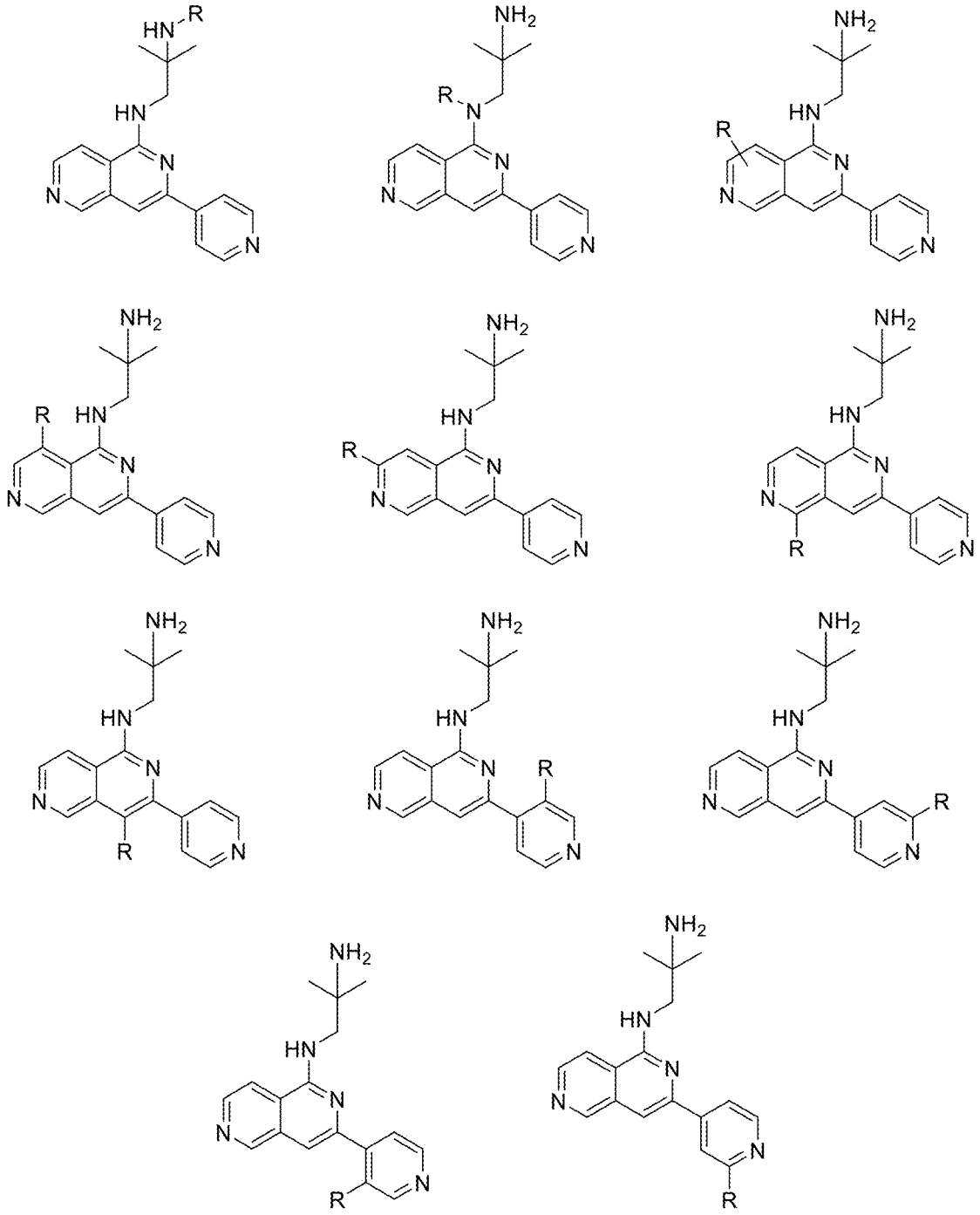


FIG. 2F

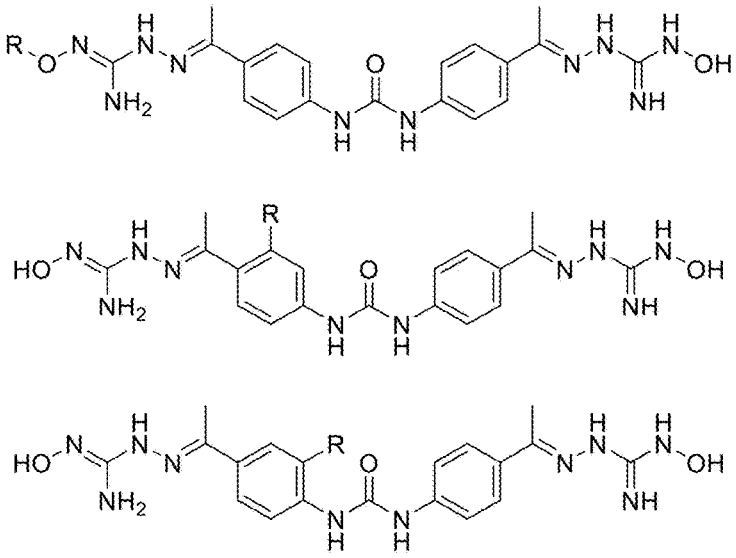


FIG. 2G

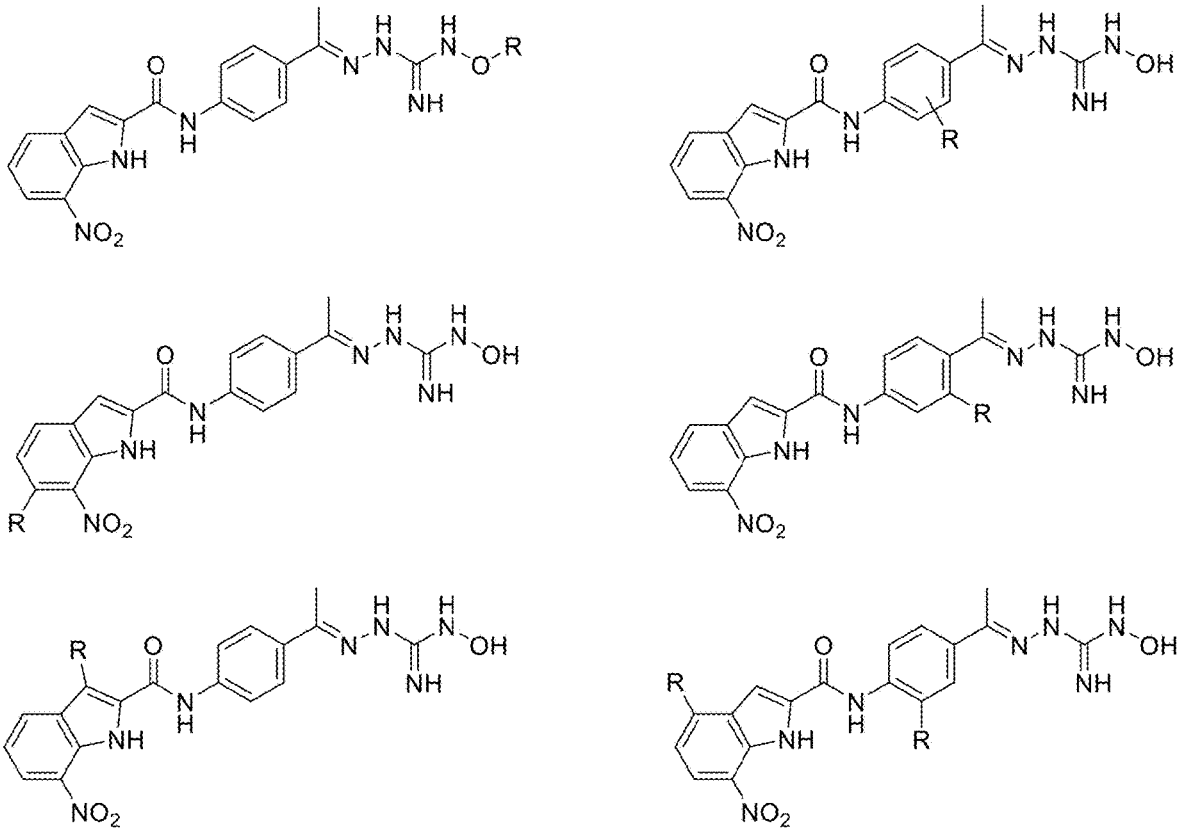


FIG. 2H

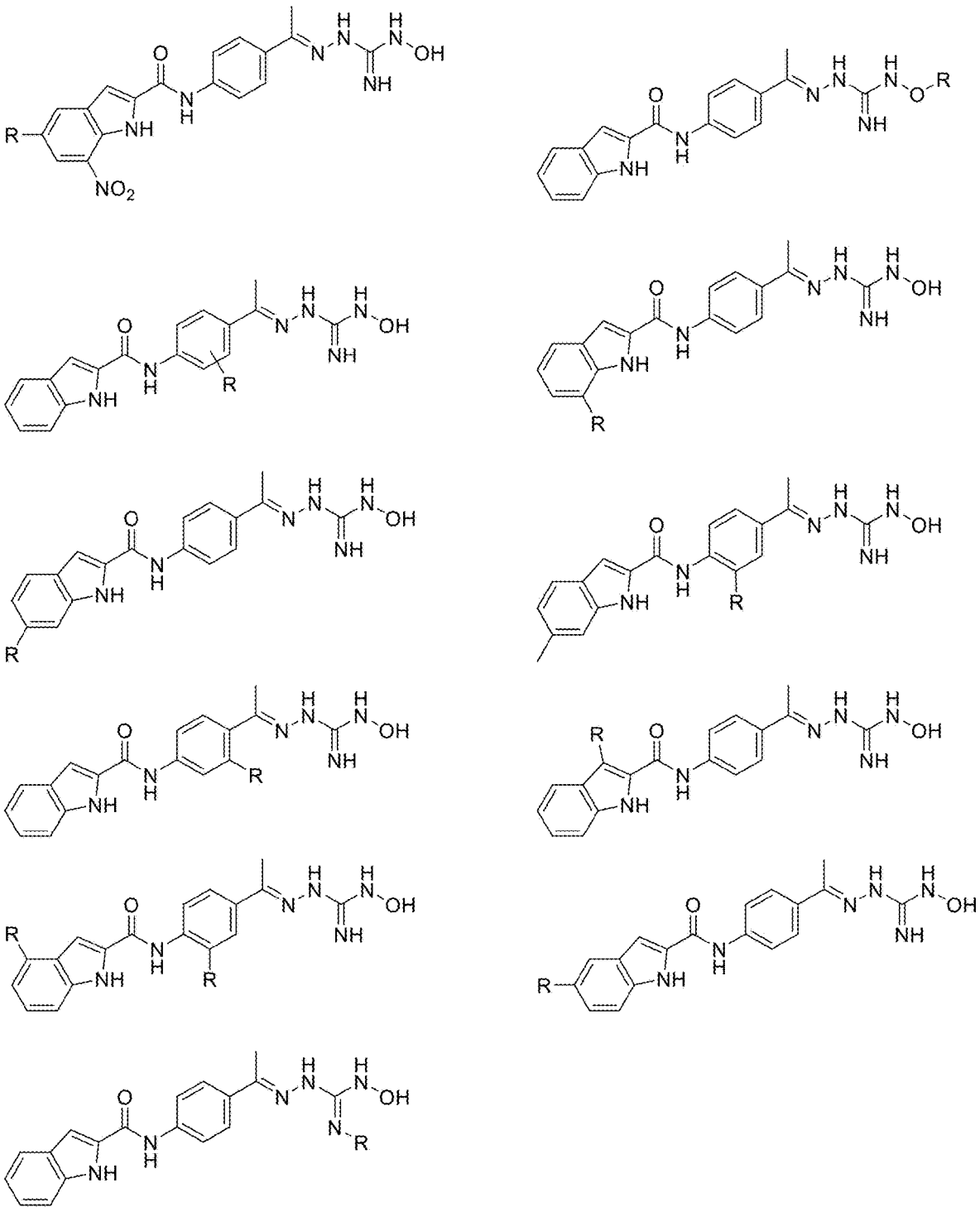
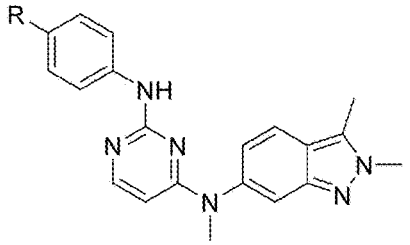
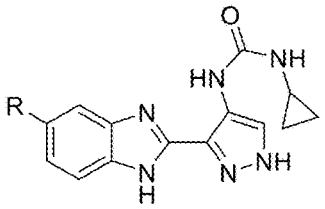


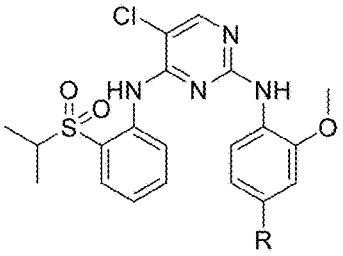
FIG. 2I



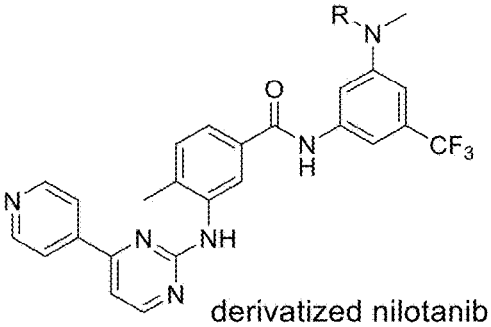
derivatized pazopanib



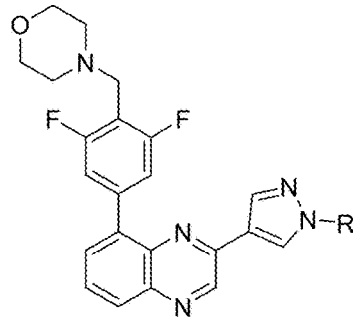
derivatized AT-9283



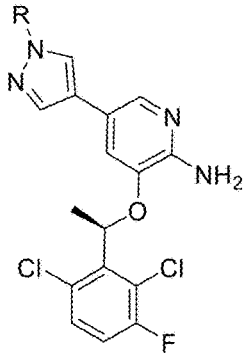
derivatized TAE684



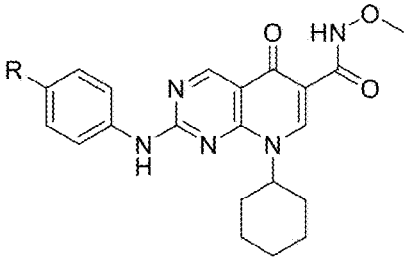
derivatized nilotanib



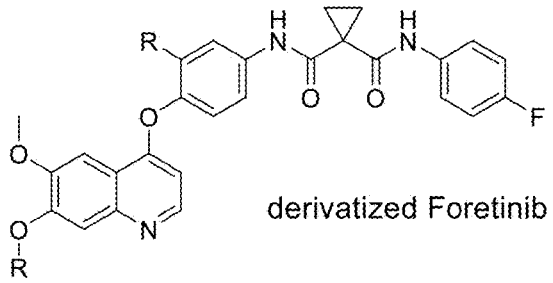
derivatized NVP-BSK805



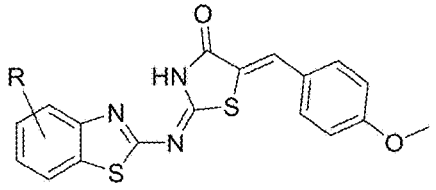
derivatized Crizotinib



derivatized JNJ FMS

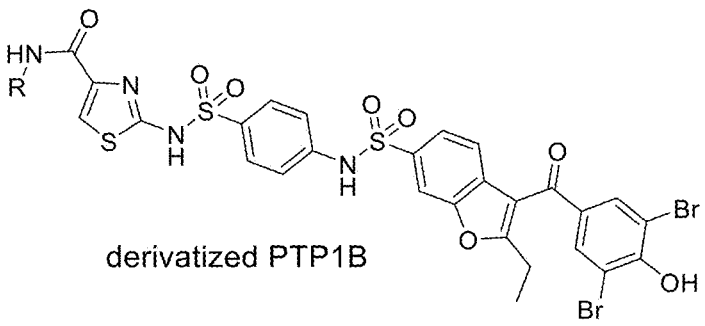


derivatized Foretinib

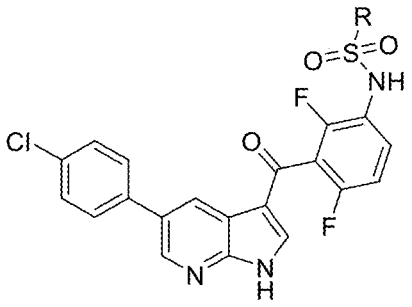


derivatized inhibitor of SHP-2 Domain of Tyrosine Phospatase

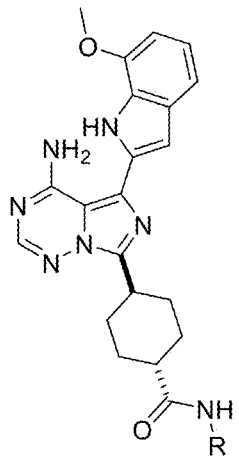
FIG. 2J



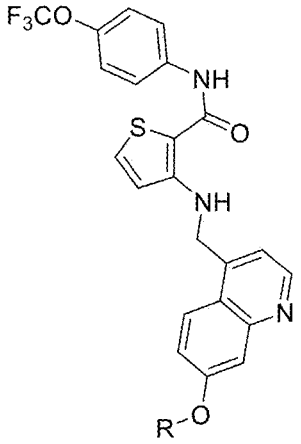
derivatized PTP1B



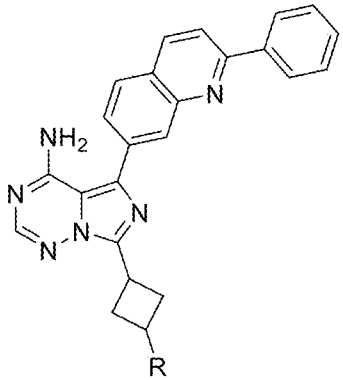
derivatized inhibitor of BRAF (BRAFV600E)/MEK



derivatized mTORC1/2 kinase inhibitor OSI-027



derivatized c-Kit/KDR kinase inhibitor OSI-930



derivatized IGF1R/IR kinase inhibitor OSI-906

FIG. 2K

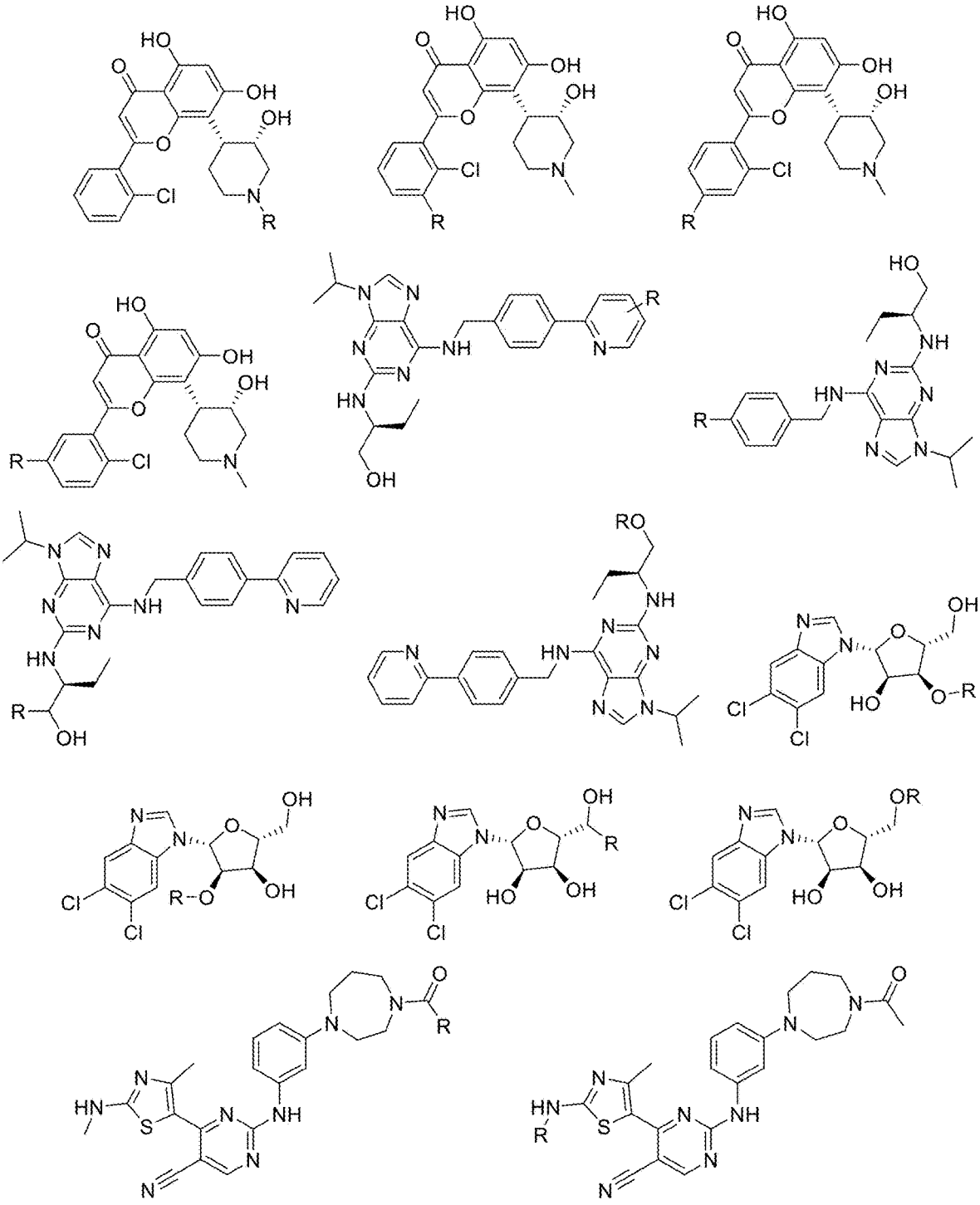


FIG. 2L

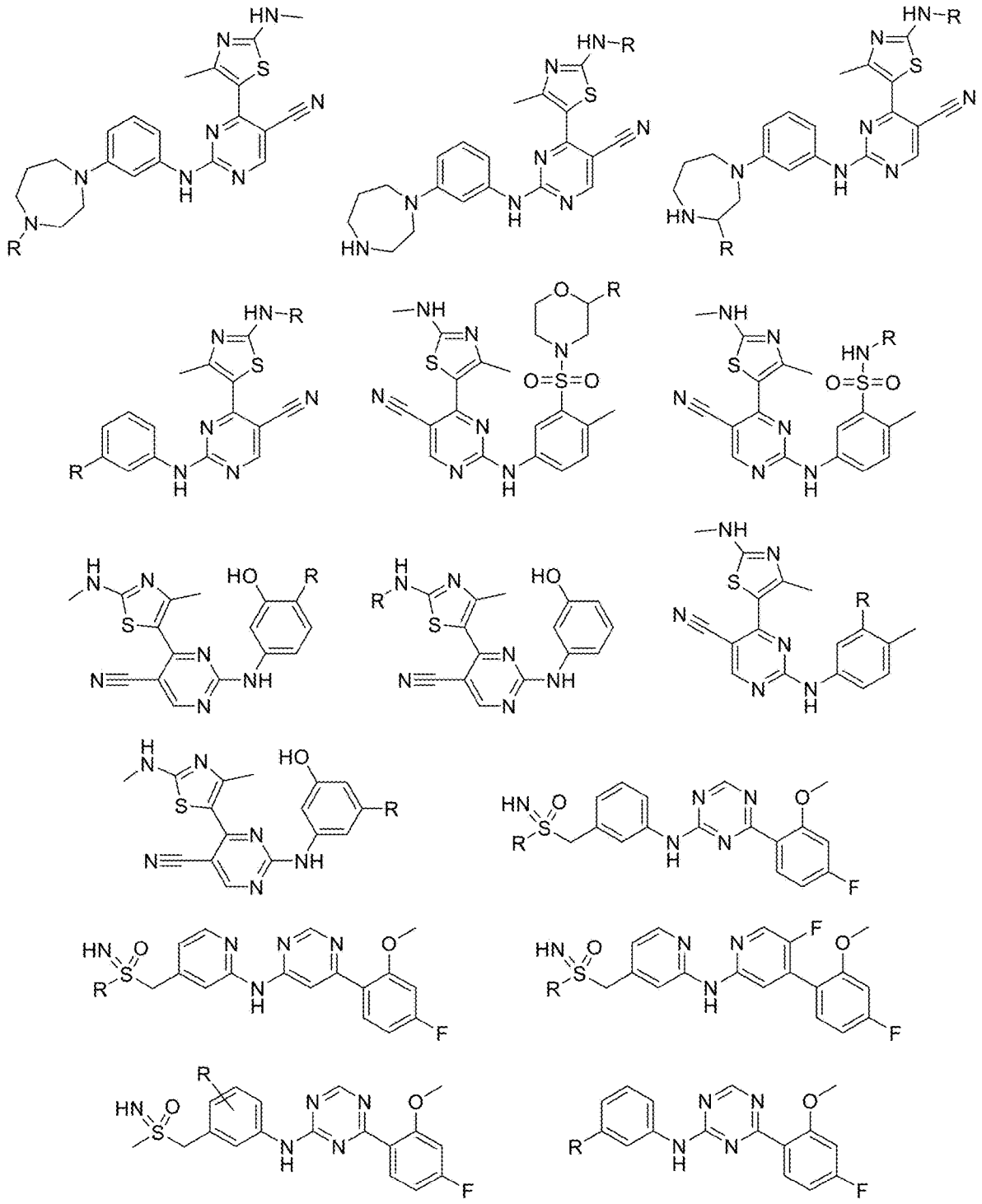


FIG. 2M

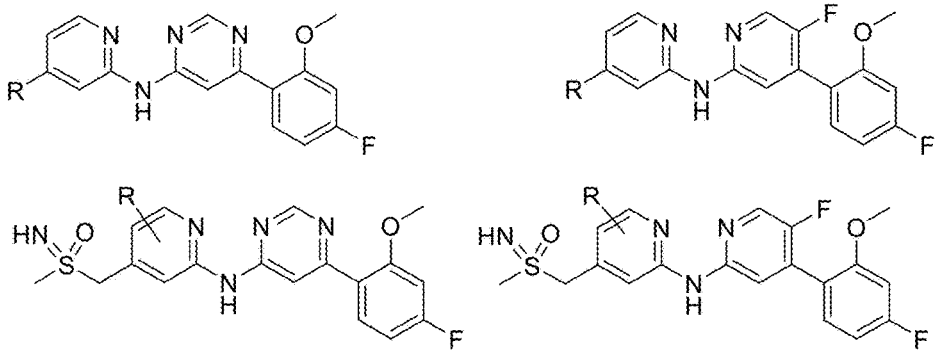


FIG. 2N

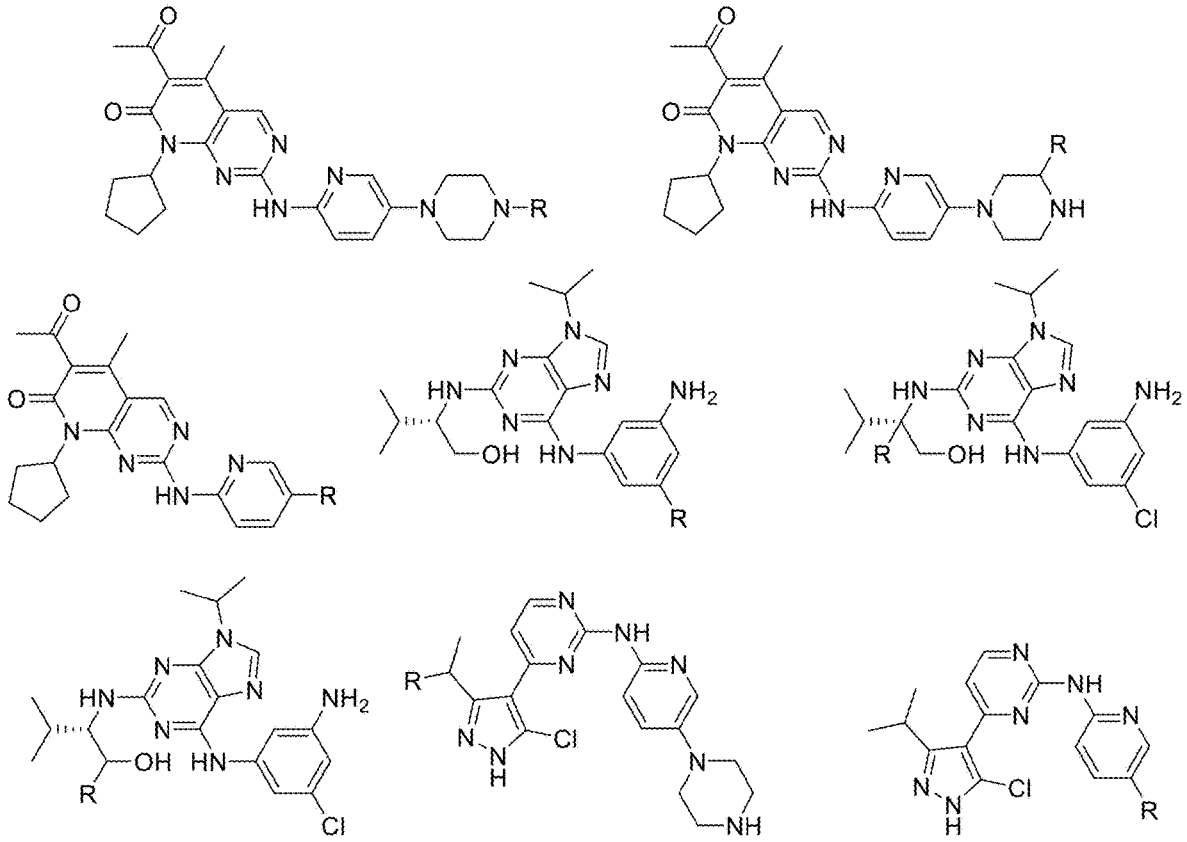


FIG. 2O

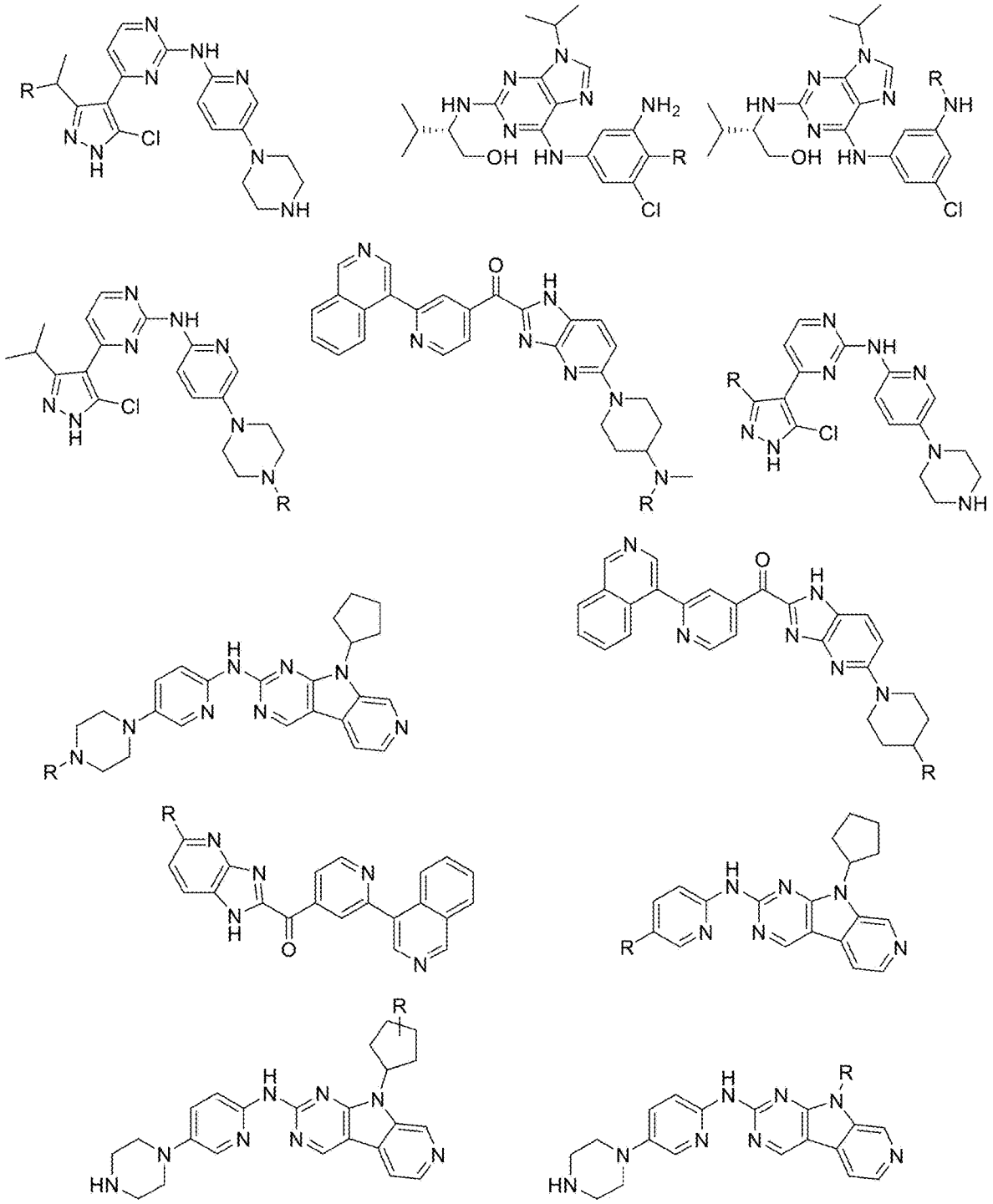


FIG. 2P

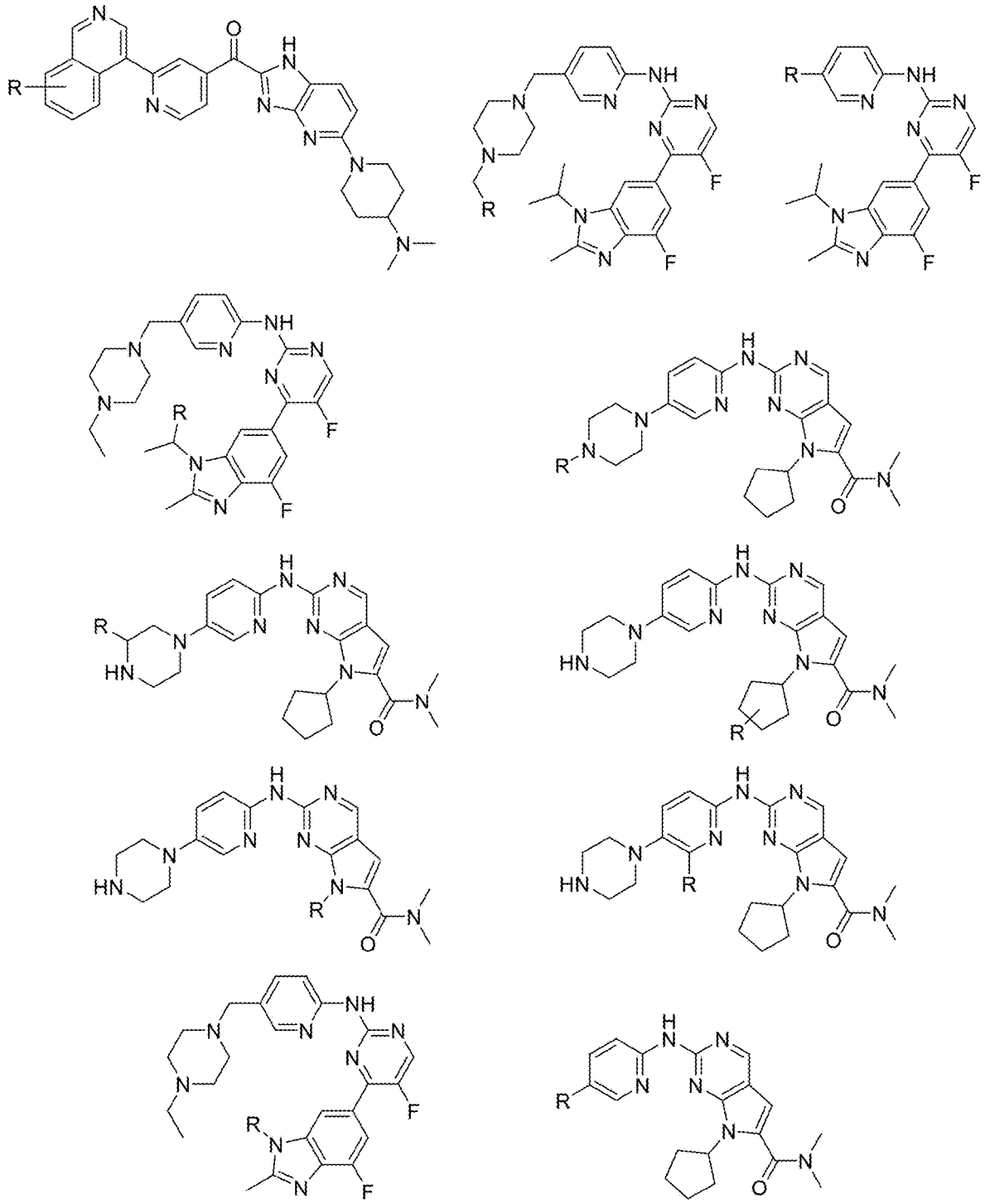


FIG. 2Q

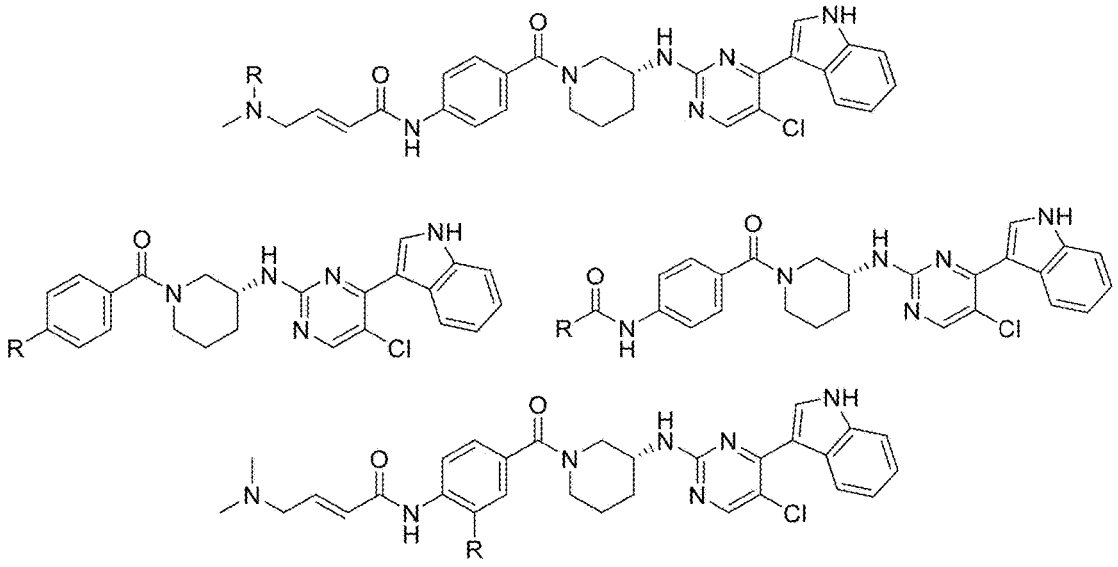


FIG. 2R

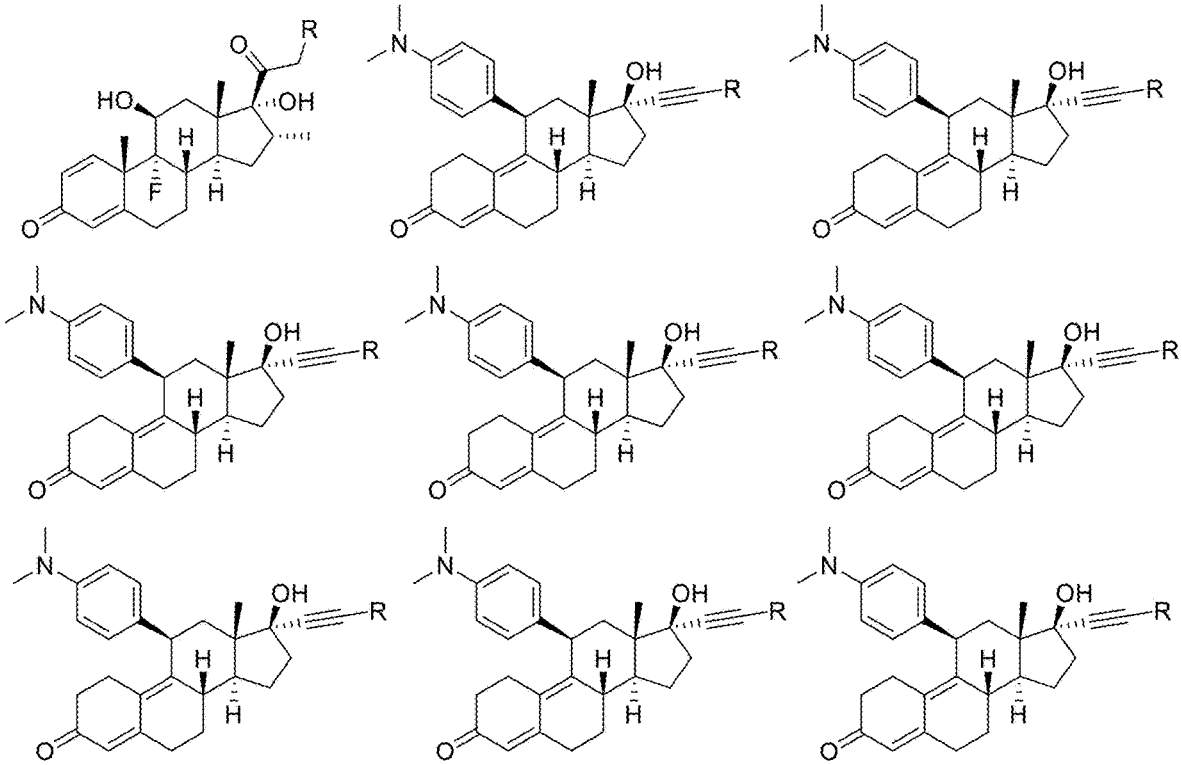


FIG. 2S

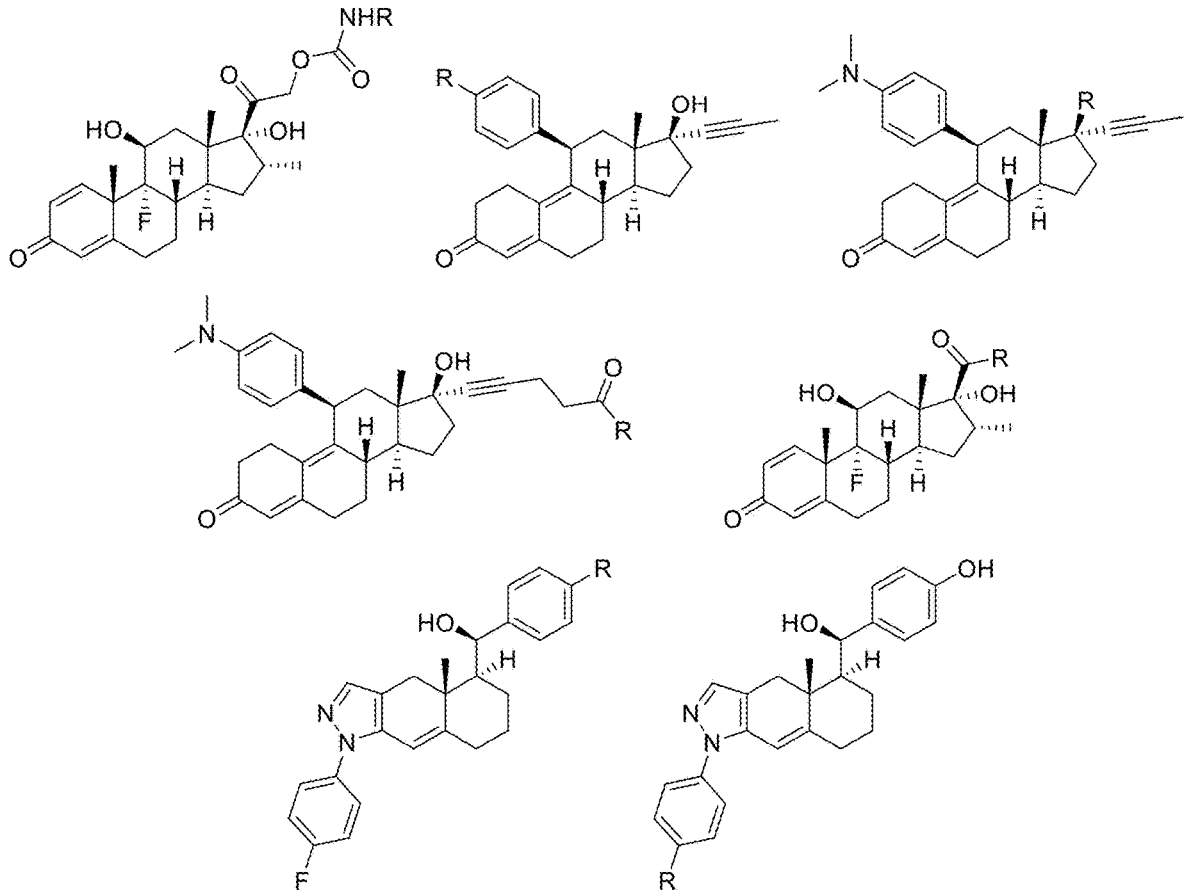


FIG. 2T

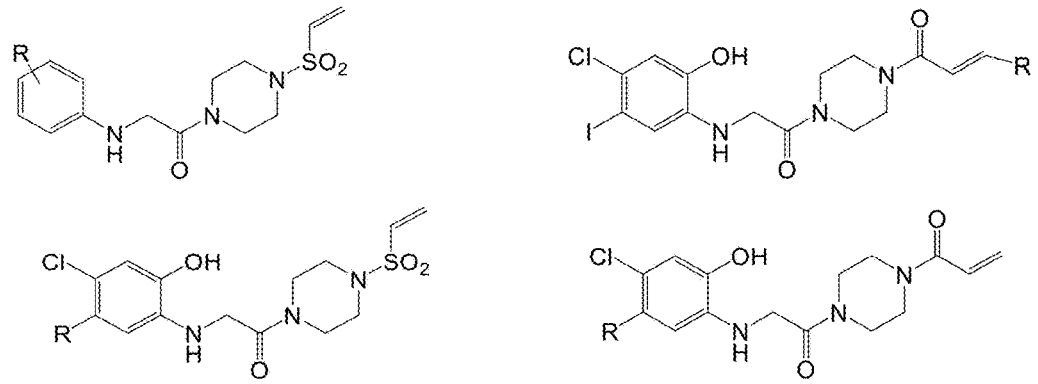


FIG. 2U

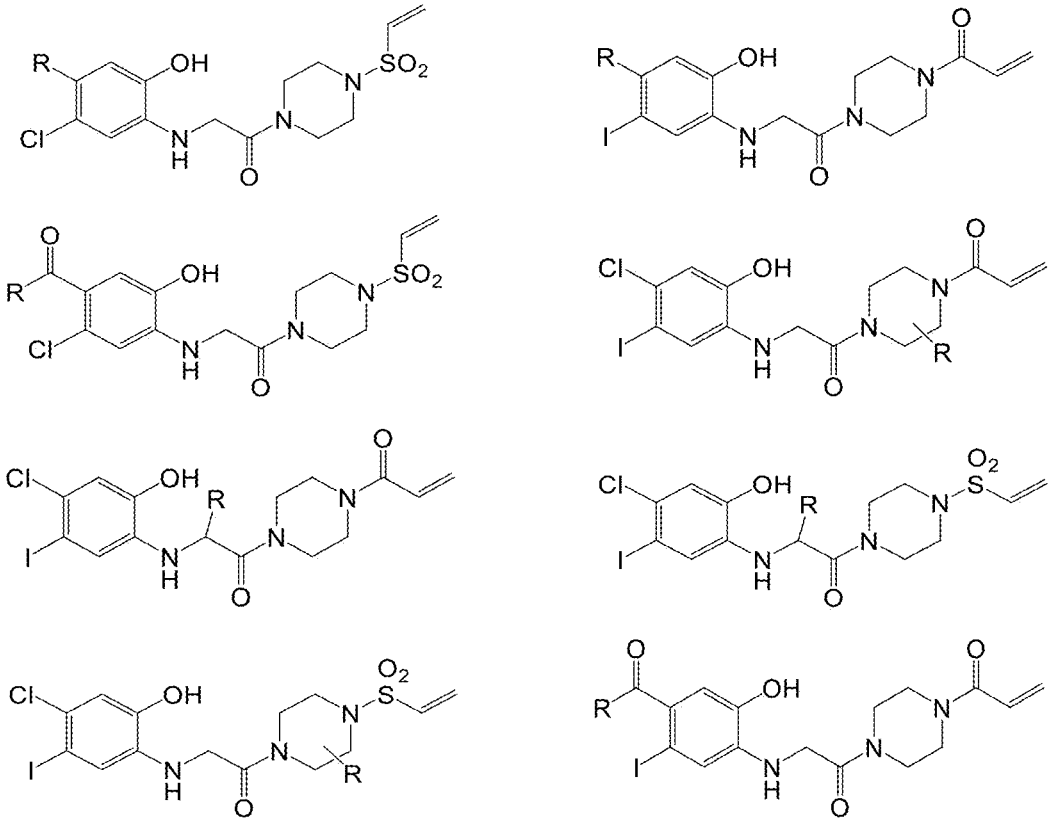

R
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FIG. 2V

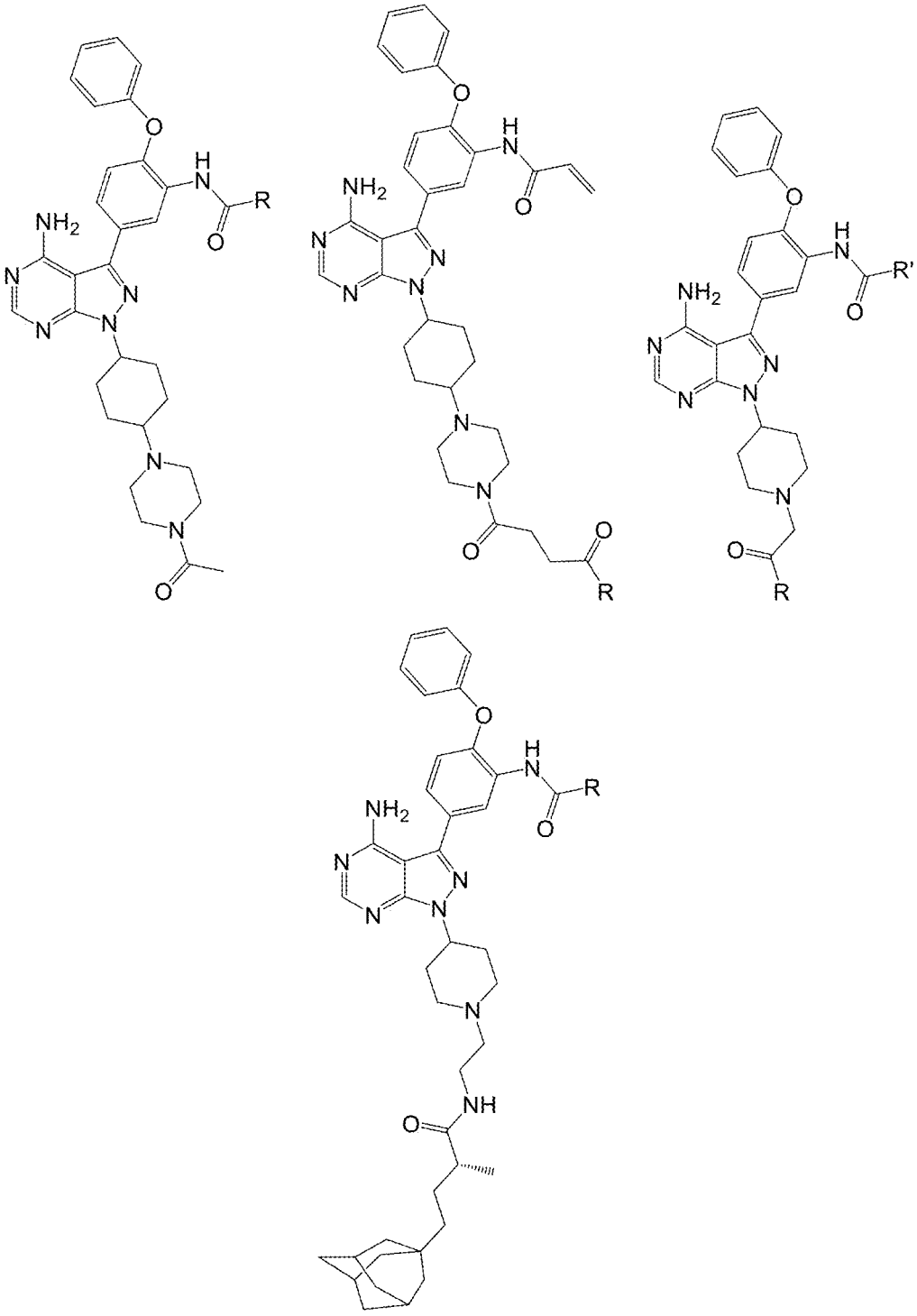

FIG. 2W

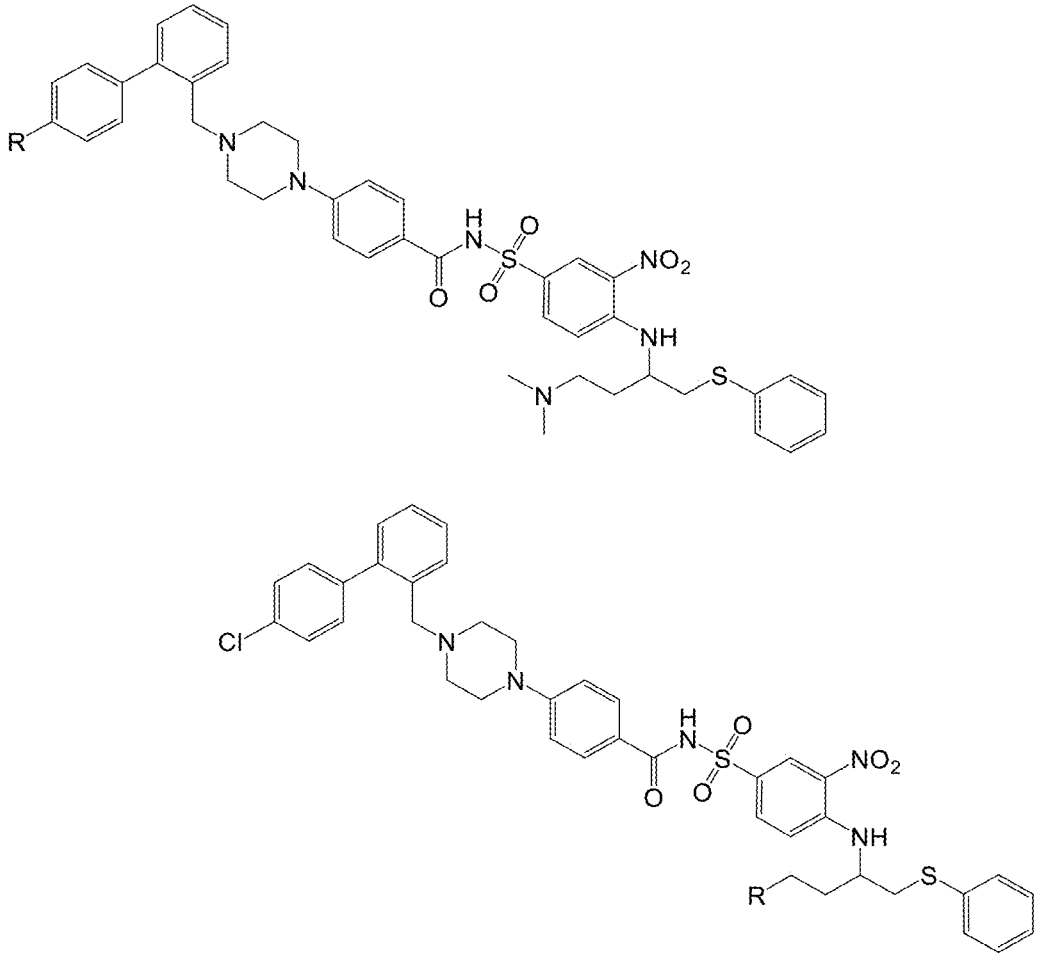

FIG. 2X

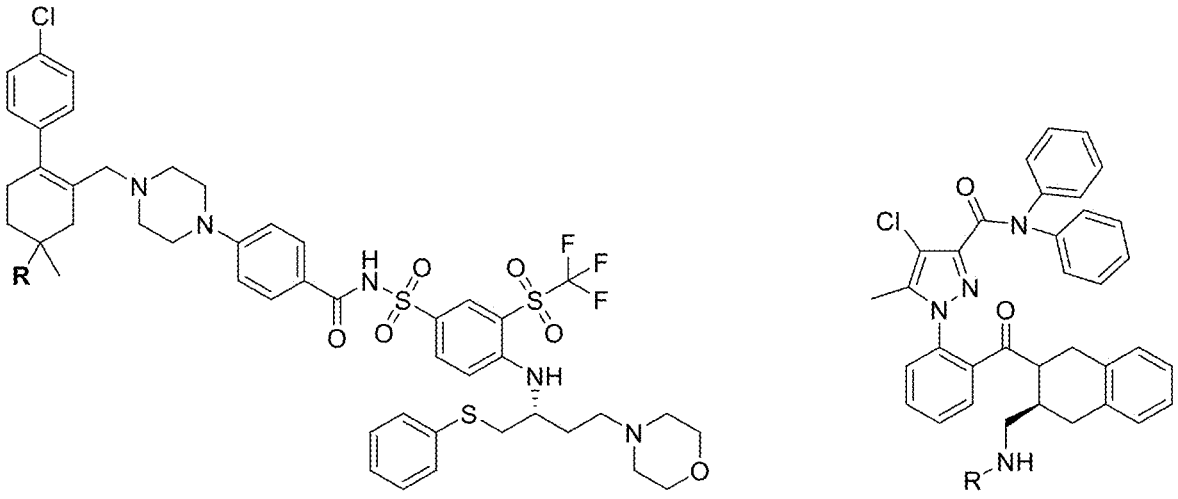

FIG. 2Y

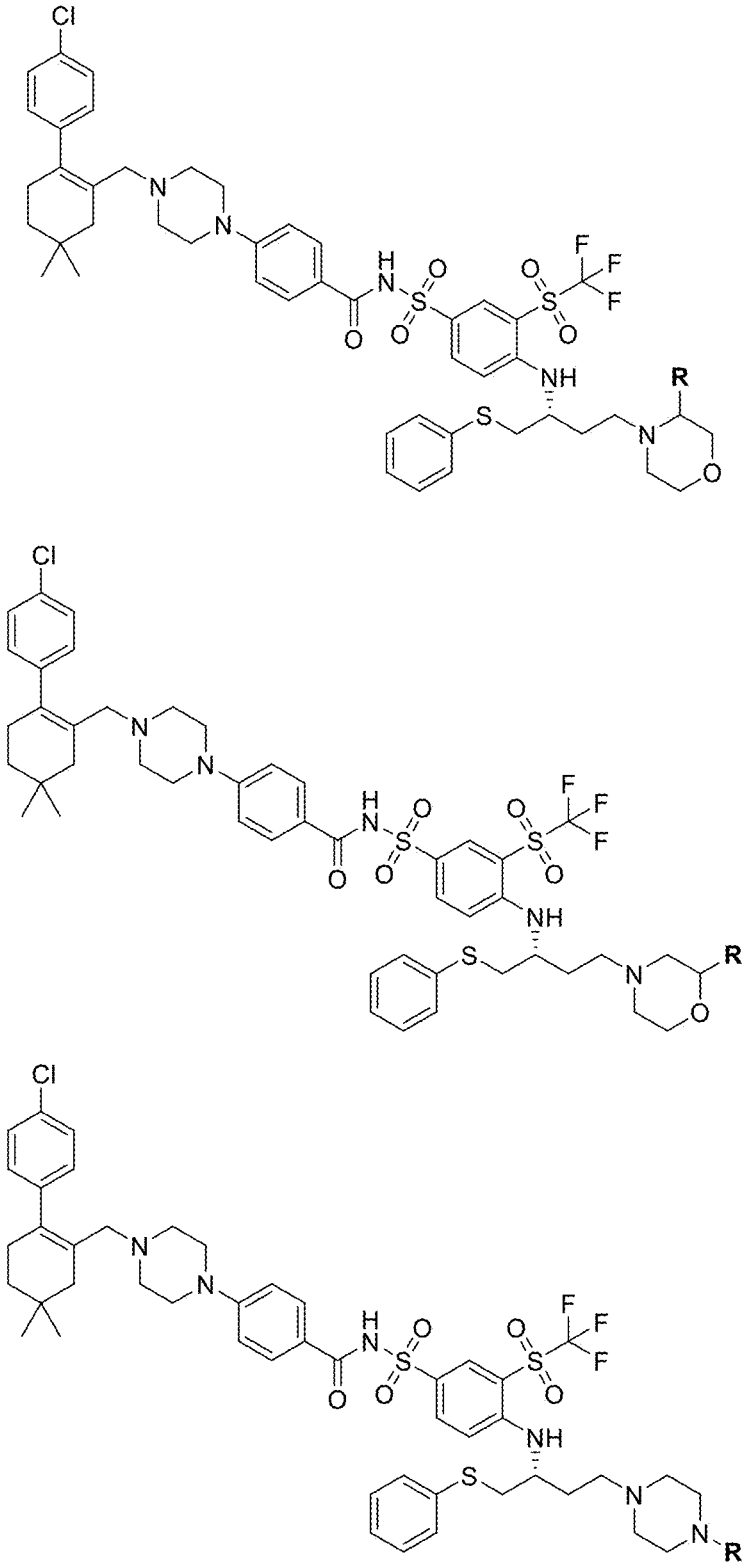
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FIG. 2Z

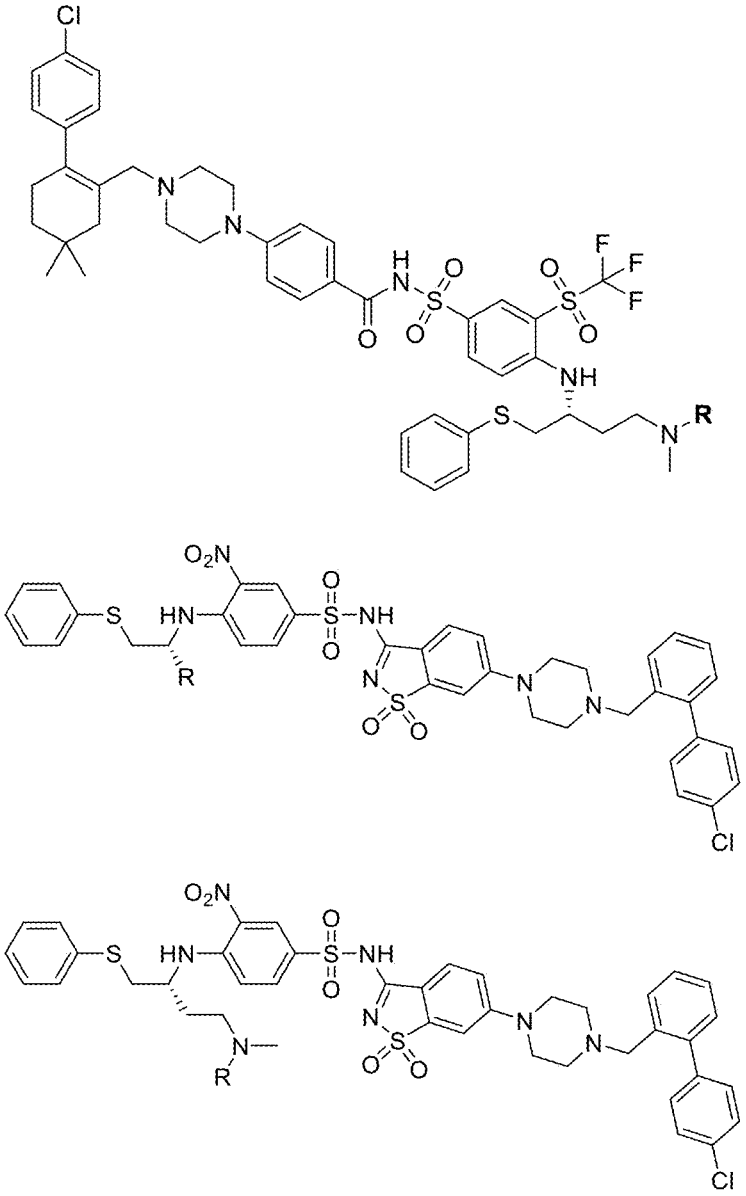
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FIG. 2AA

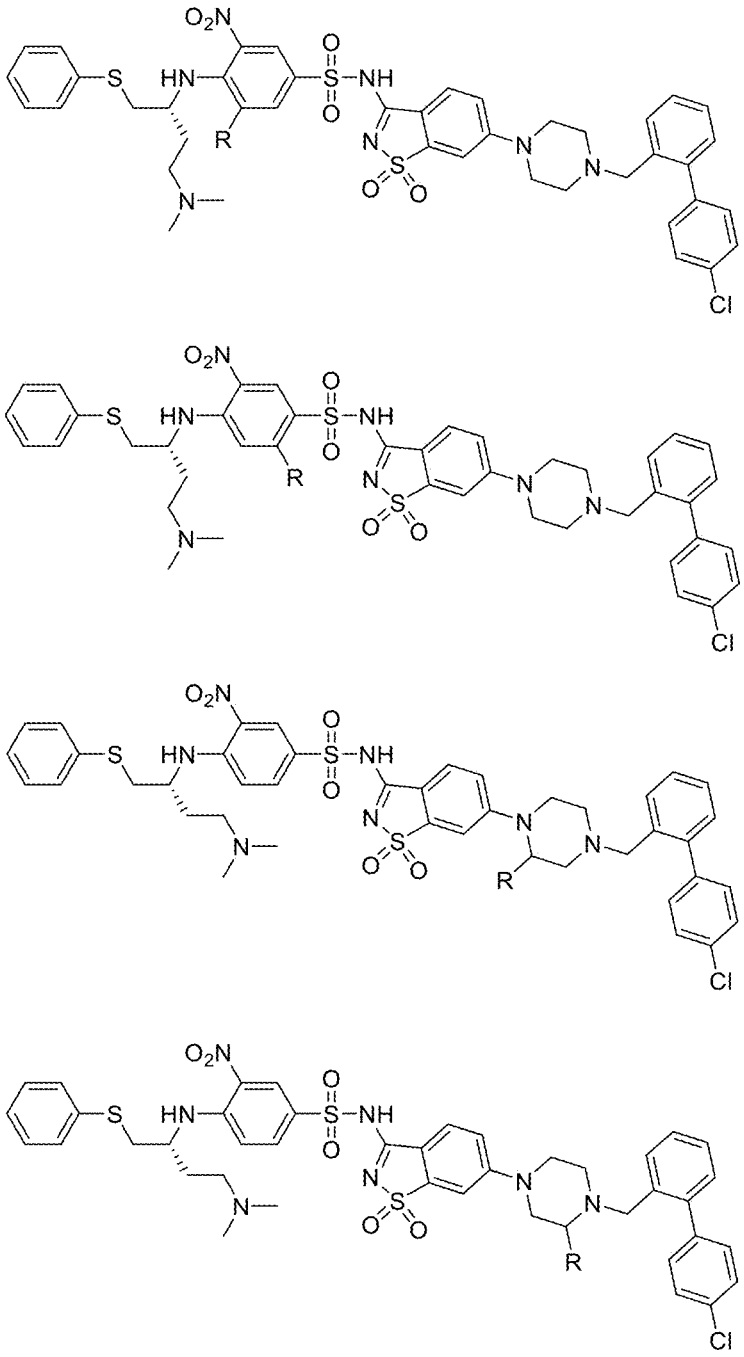
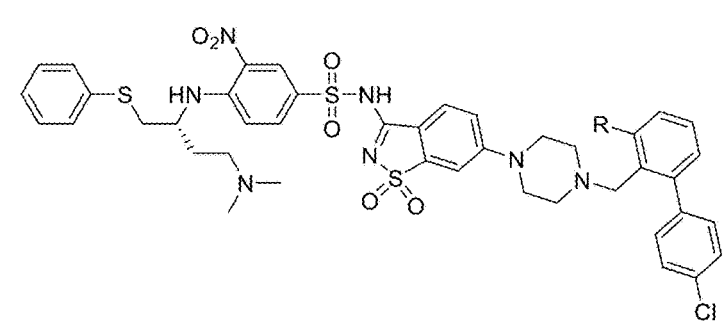
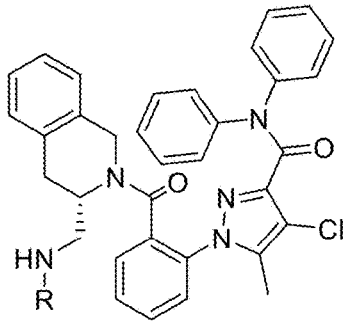
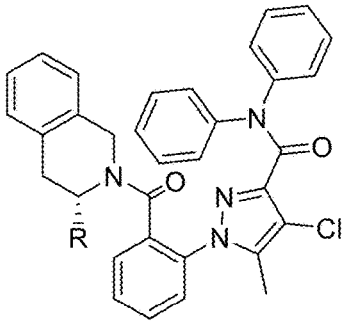
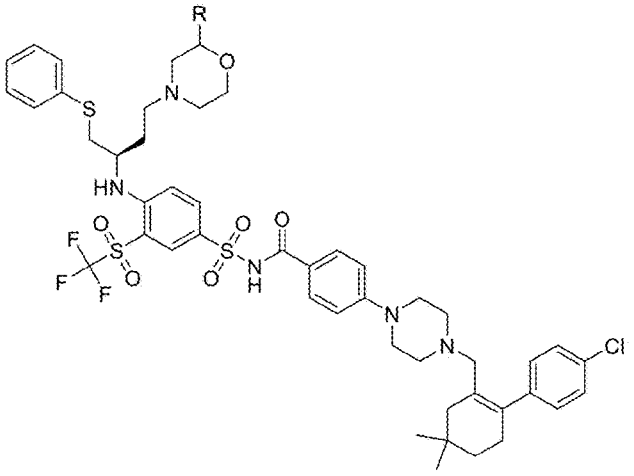


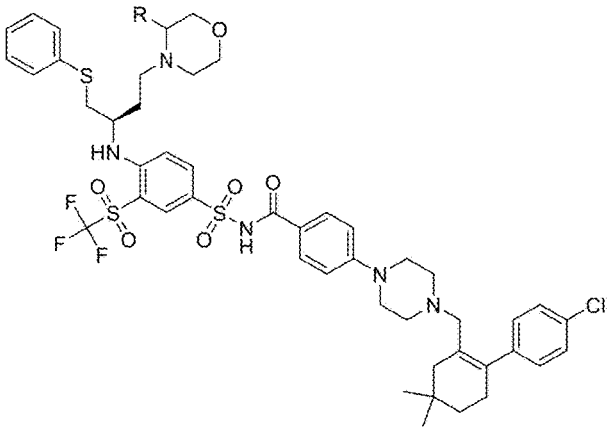
FIG. 2BB











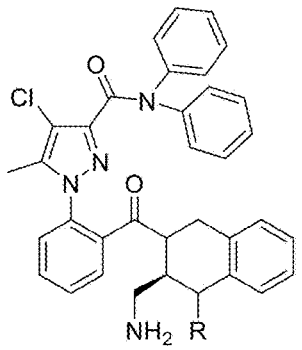


FIG. 2CC

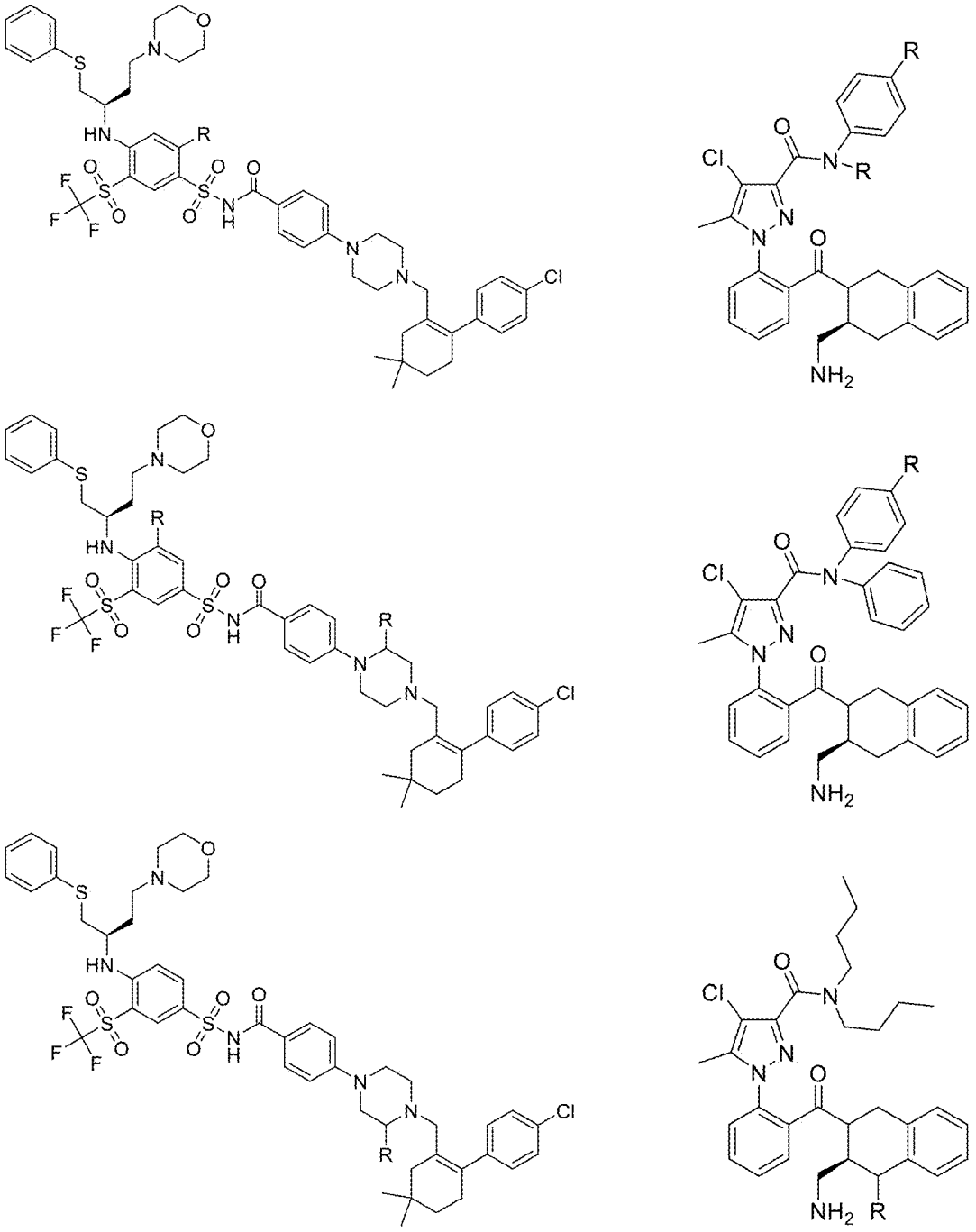


FIG. 2DD

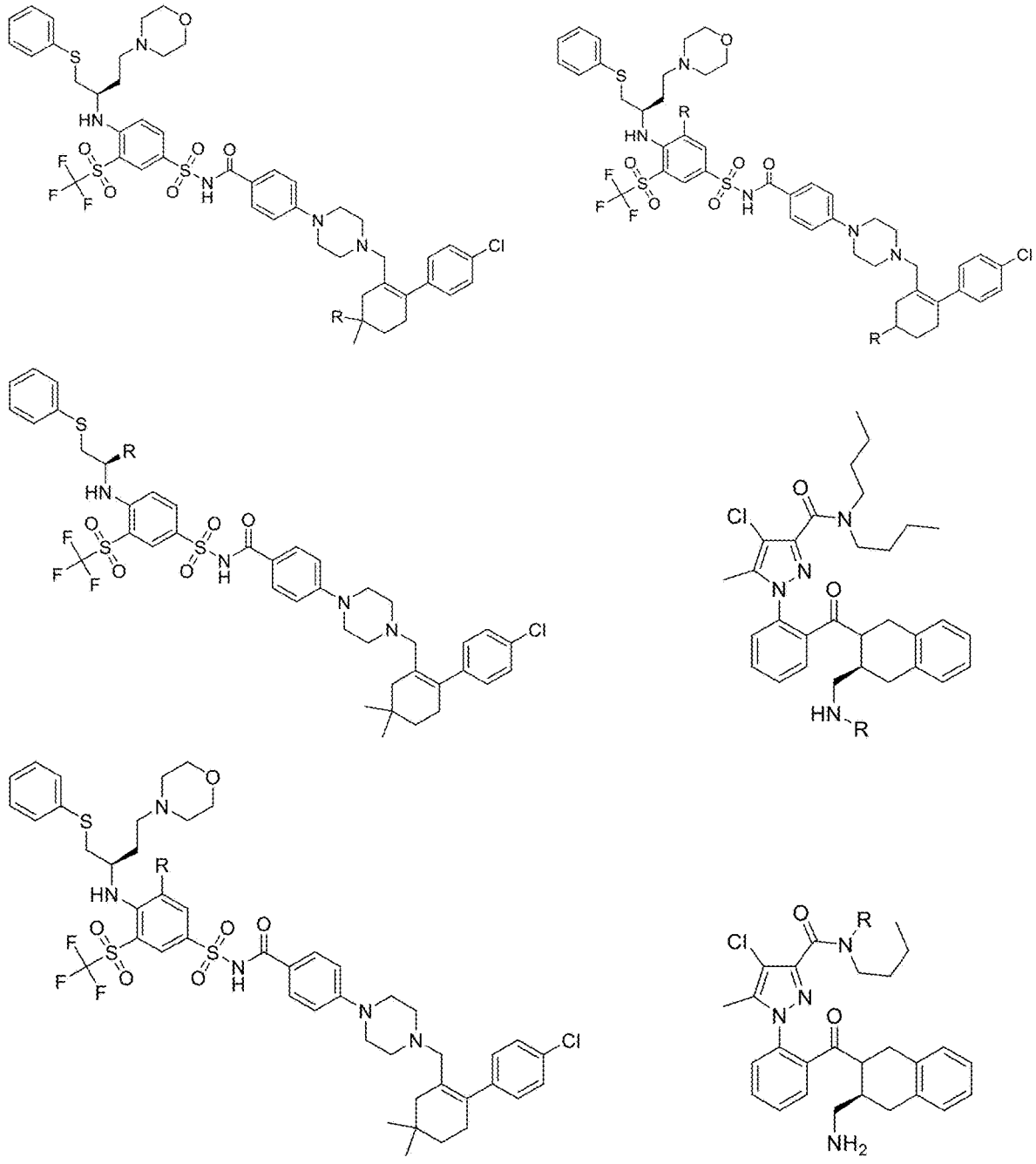


FIG. 2EE

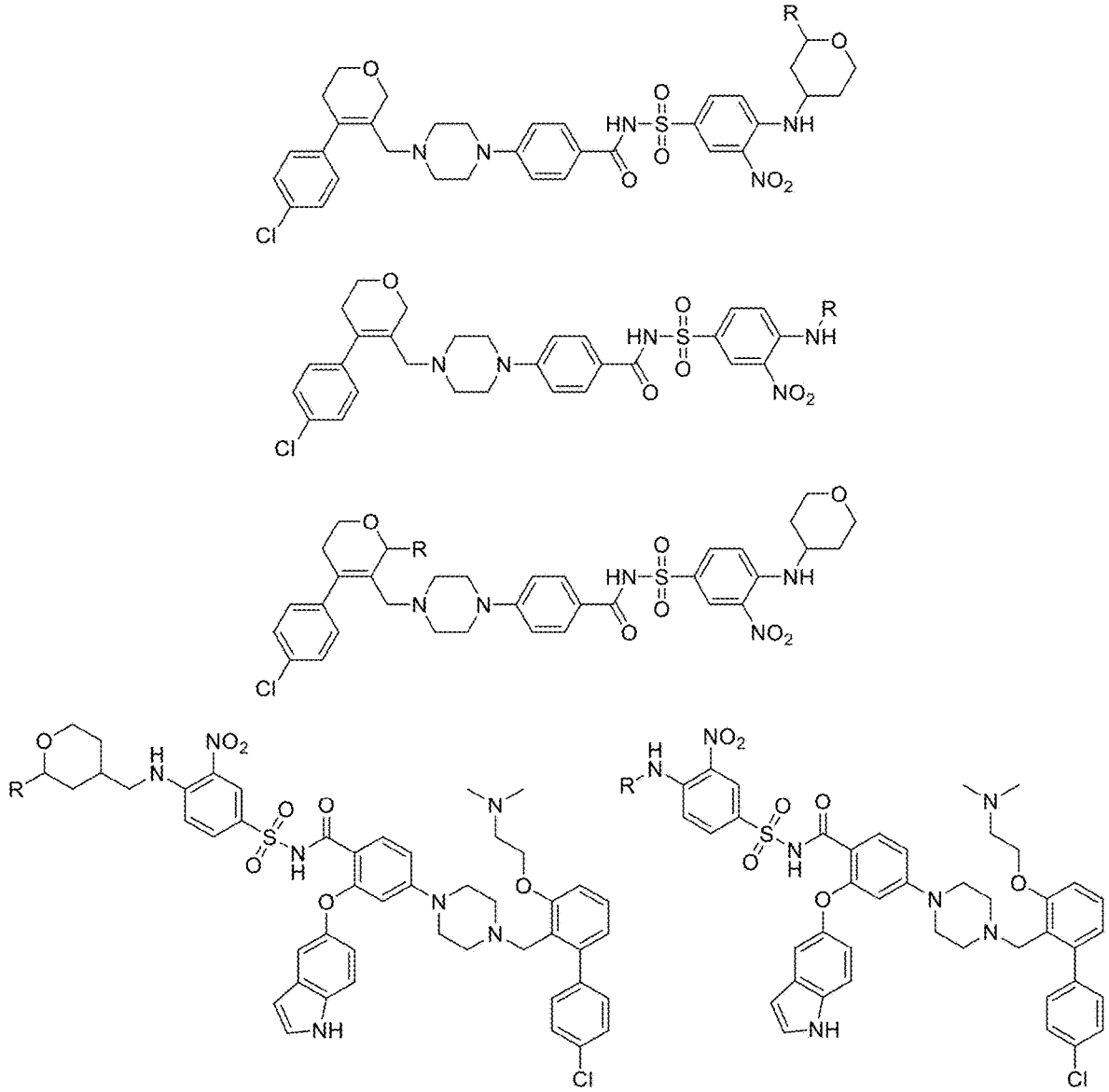


FIG. 2FF

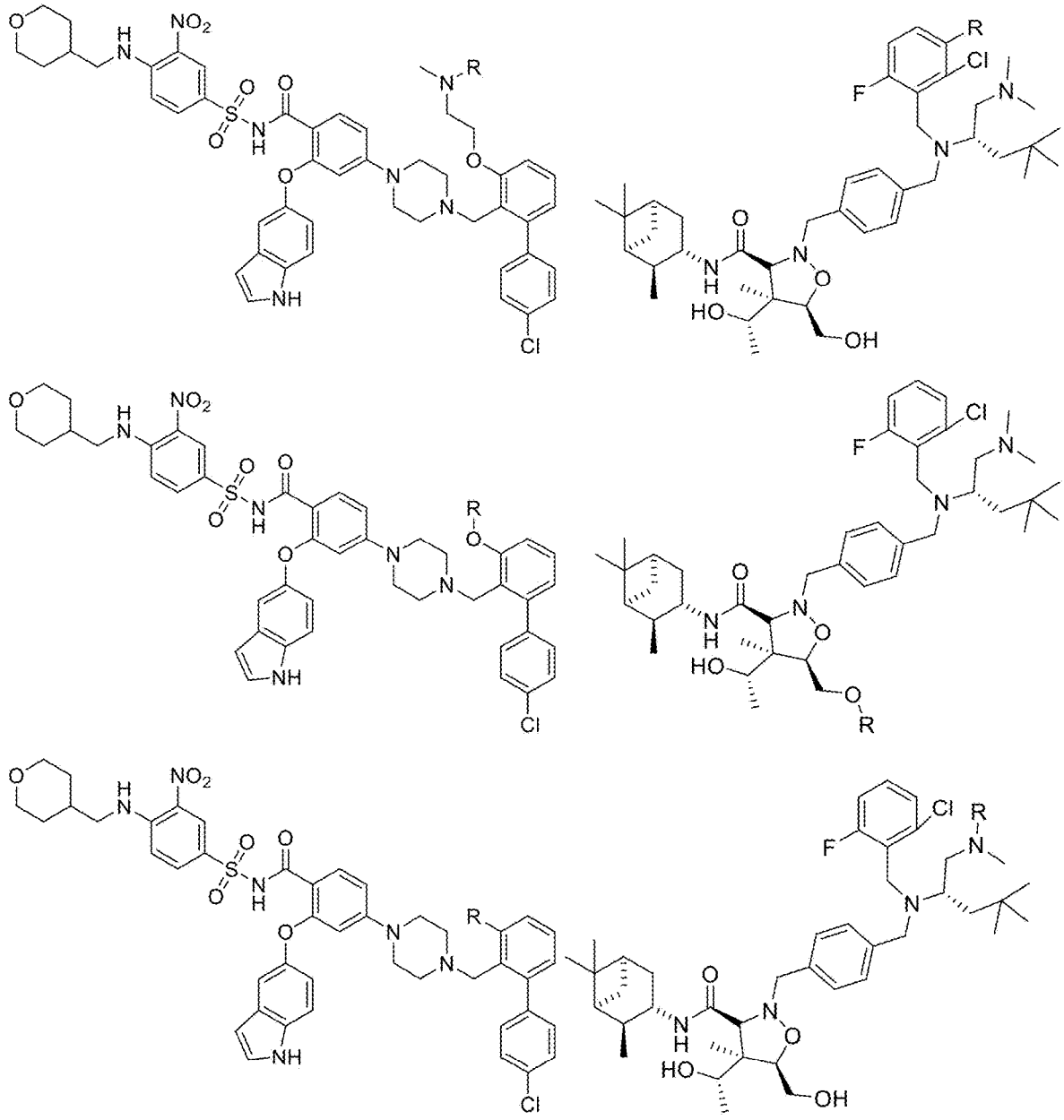


FIG. 2GG

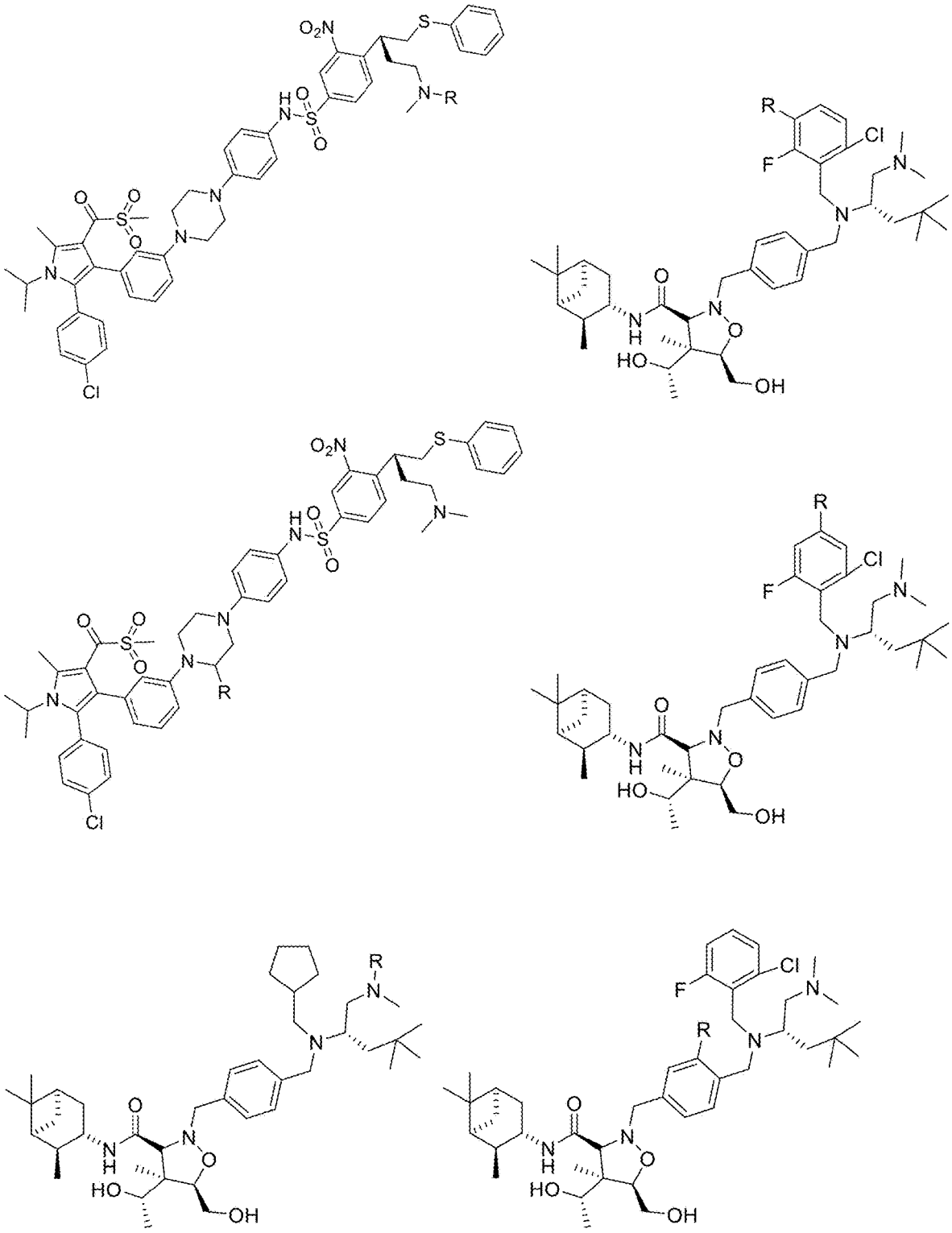


FIG. 2HH

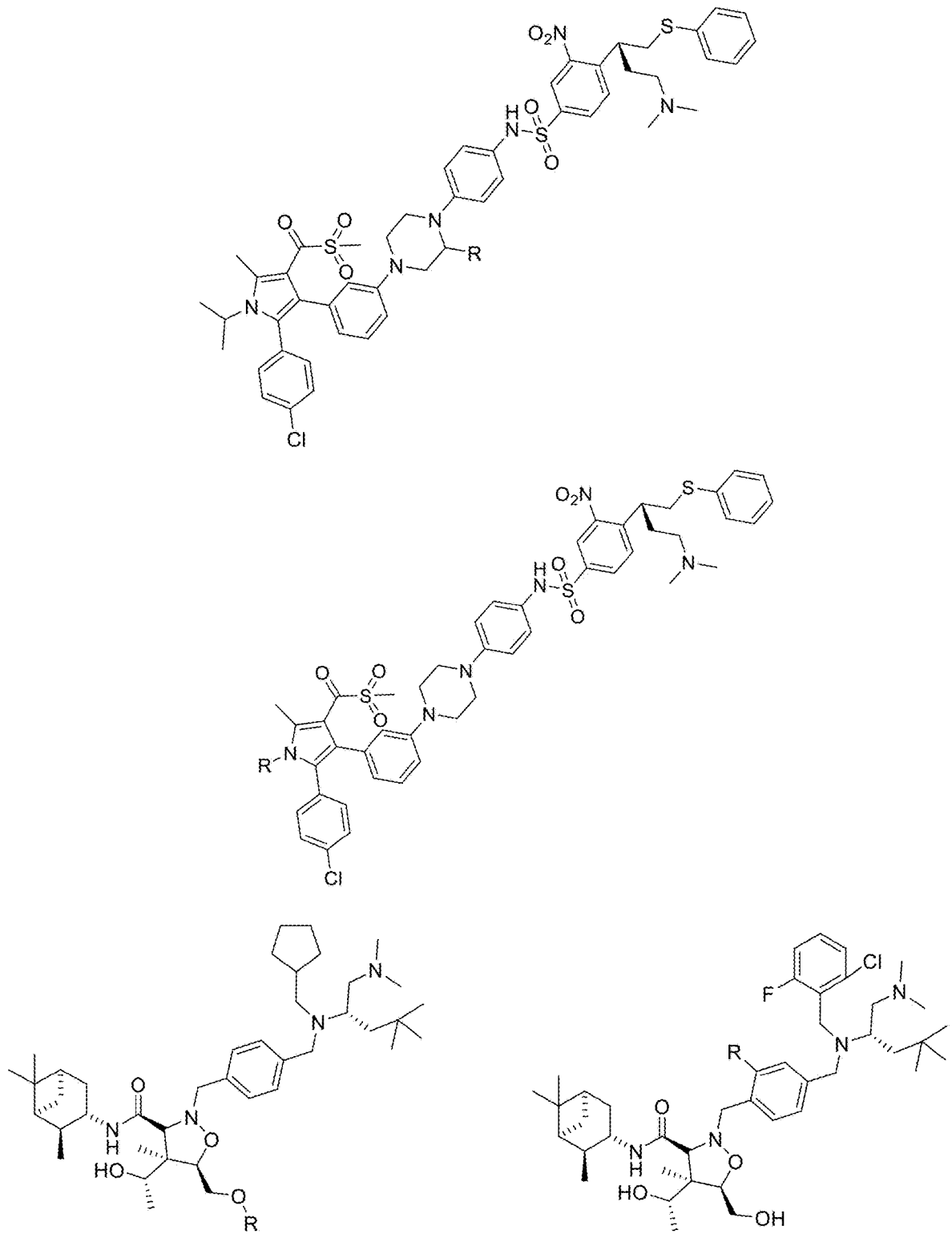


FIG. 2II

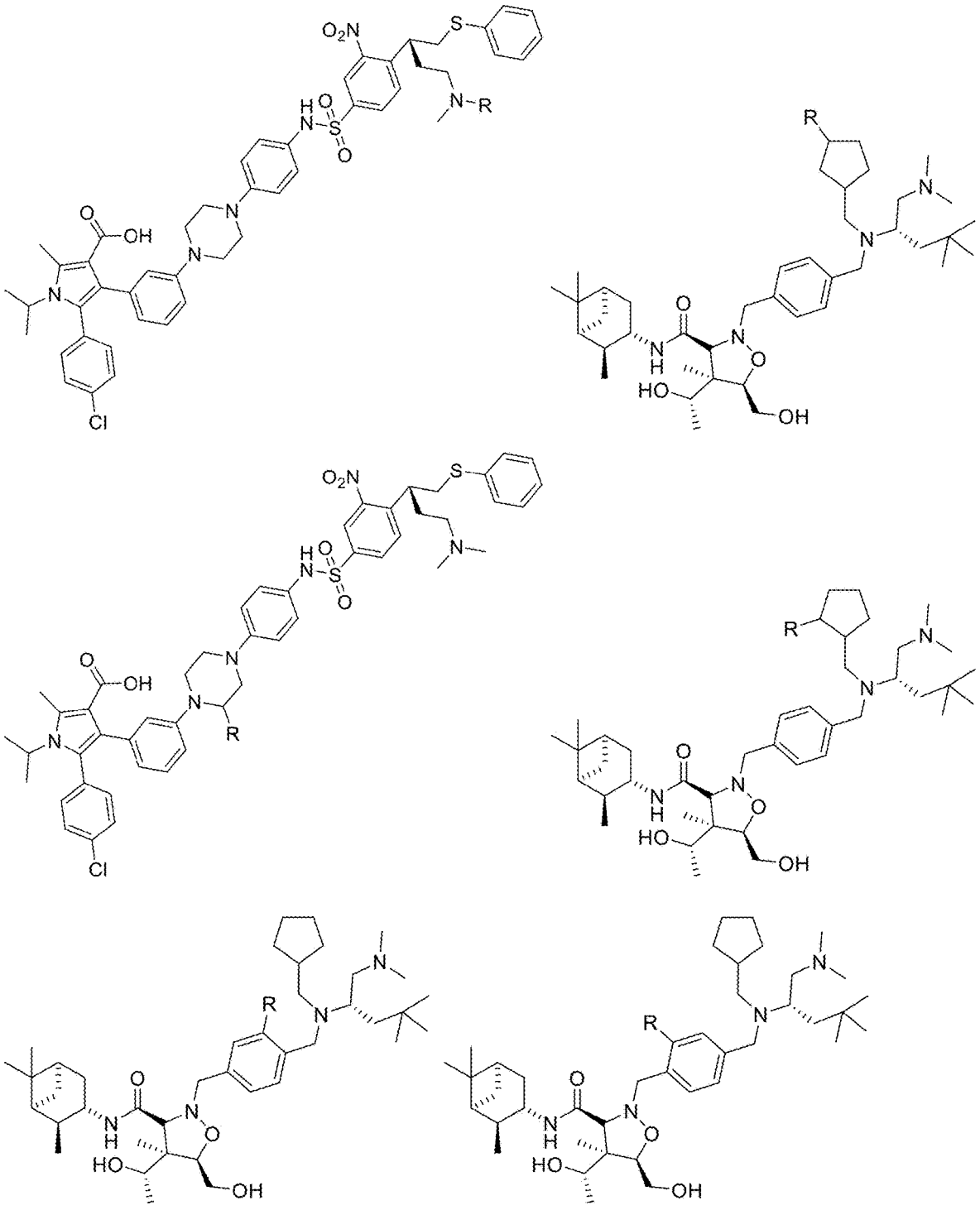


FIG. 2JJ

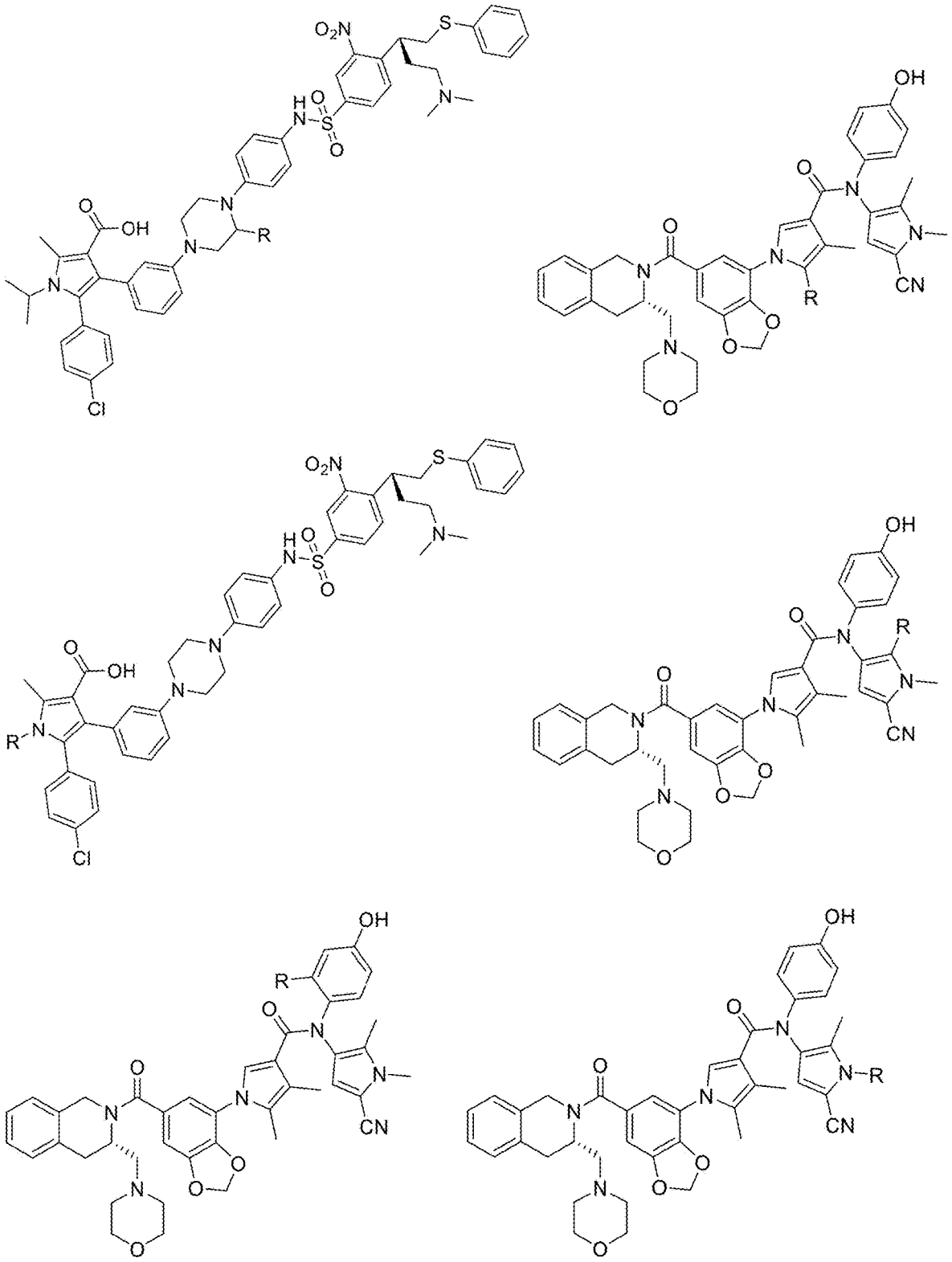


FIG. 2KK

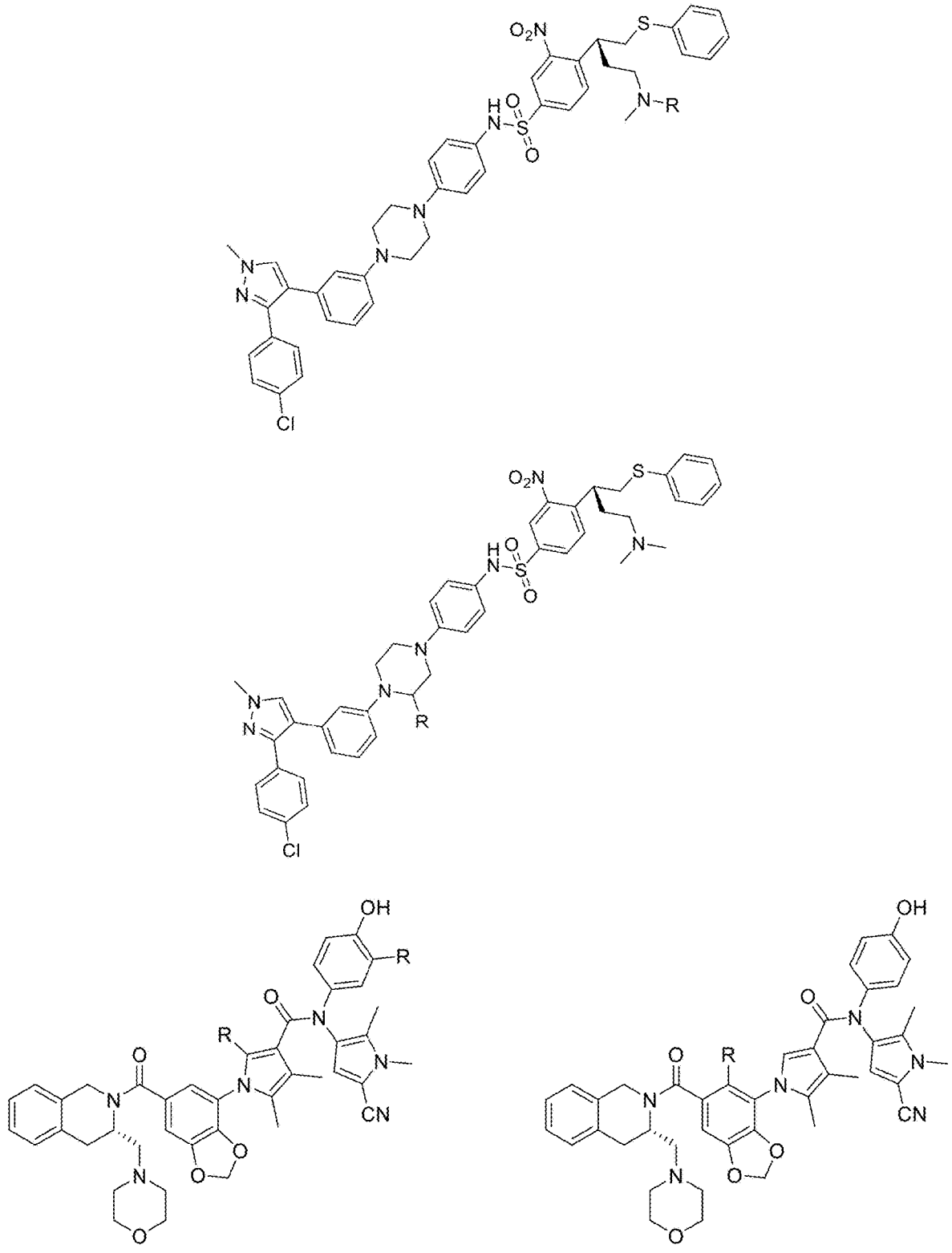


FIG. 2LL

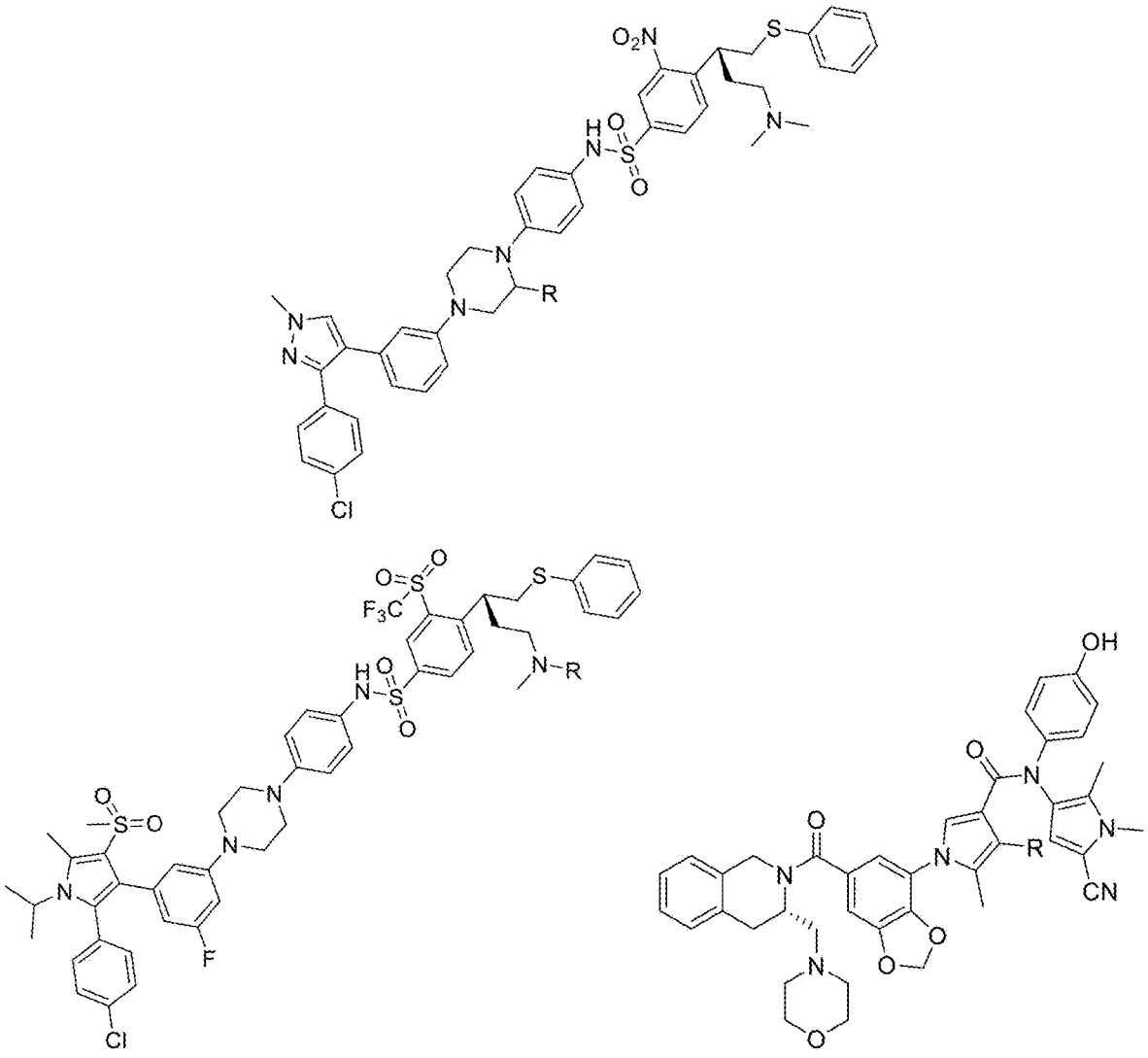


FIG. 2MM

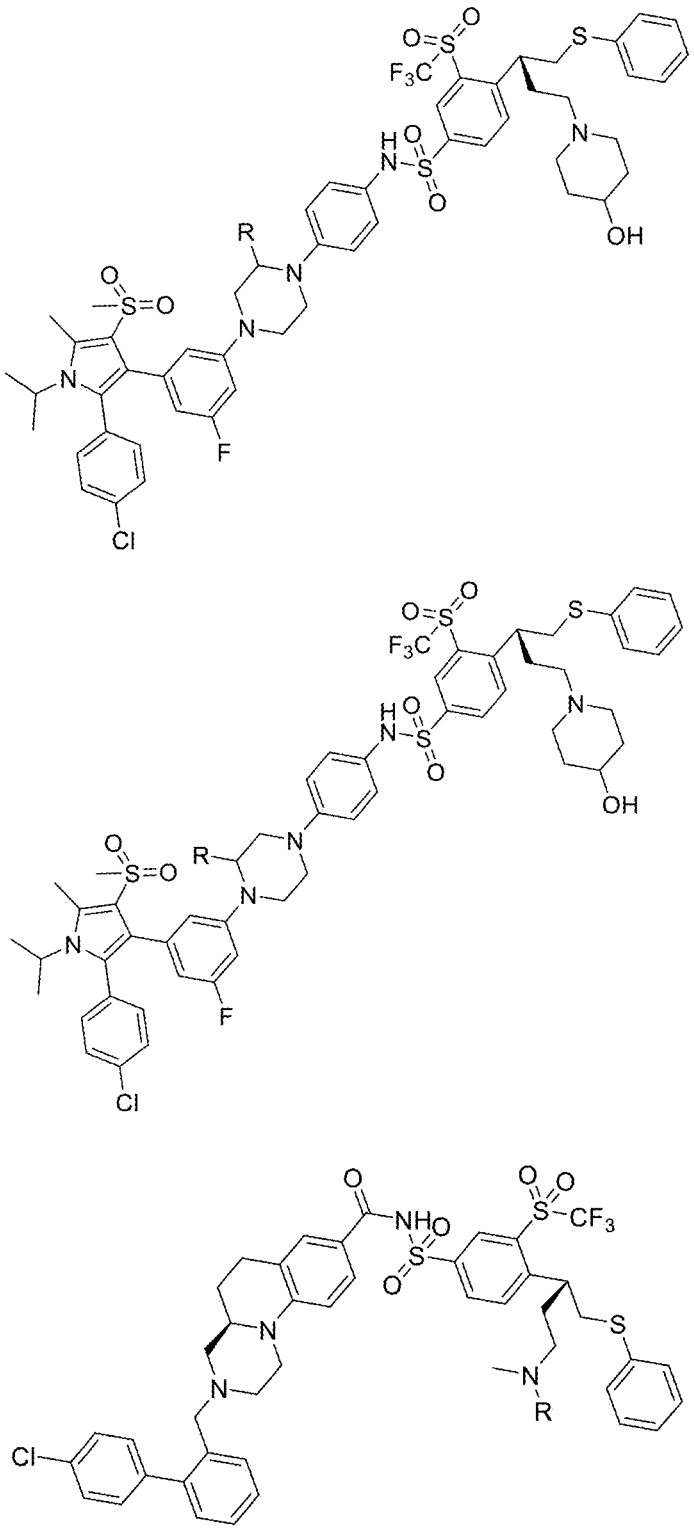


FIG. 2NN

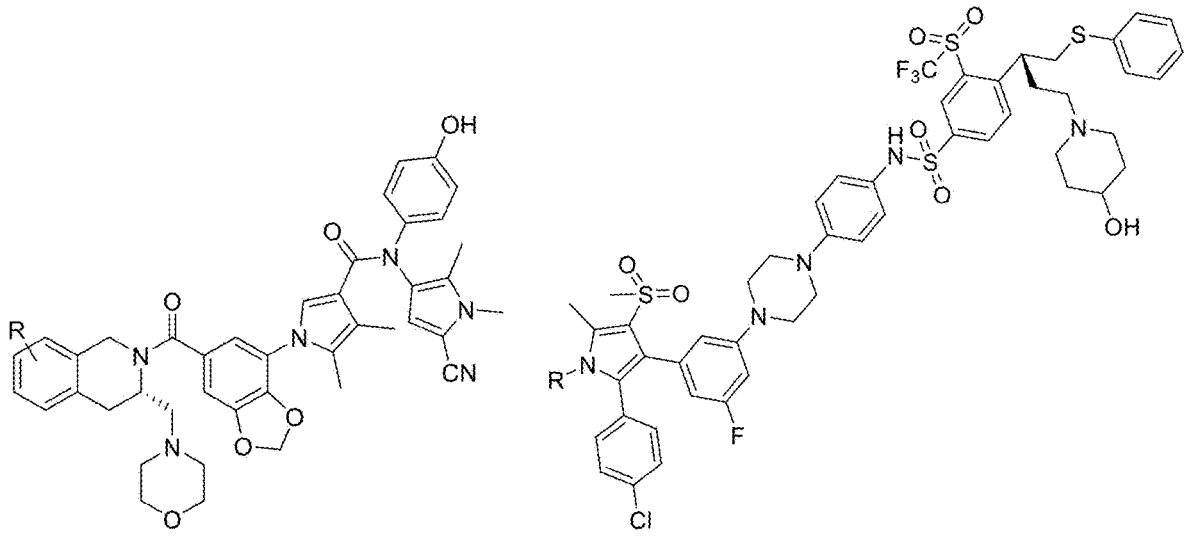


FIG. 2OO

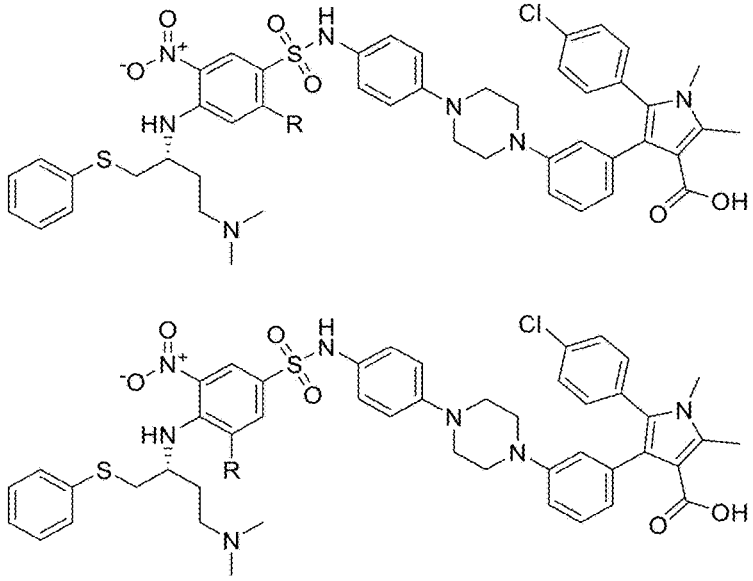


FIG. 2PP

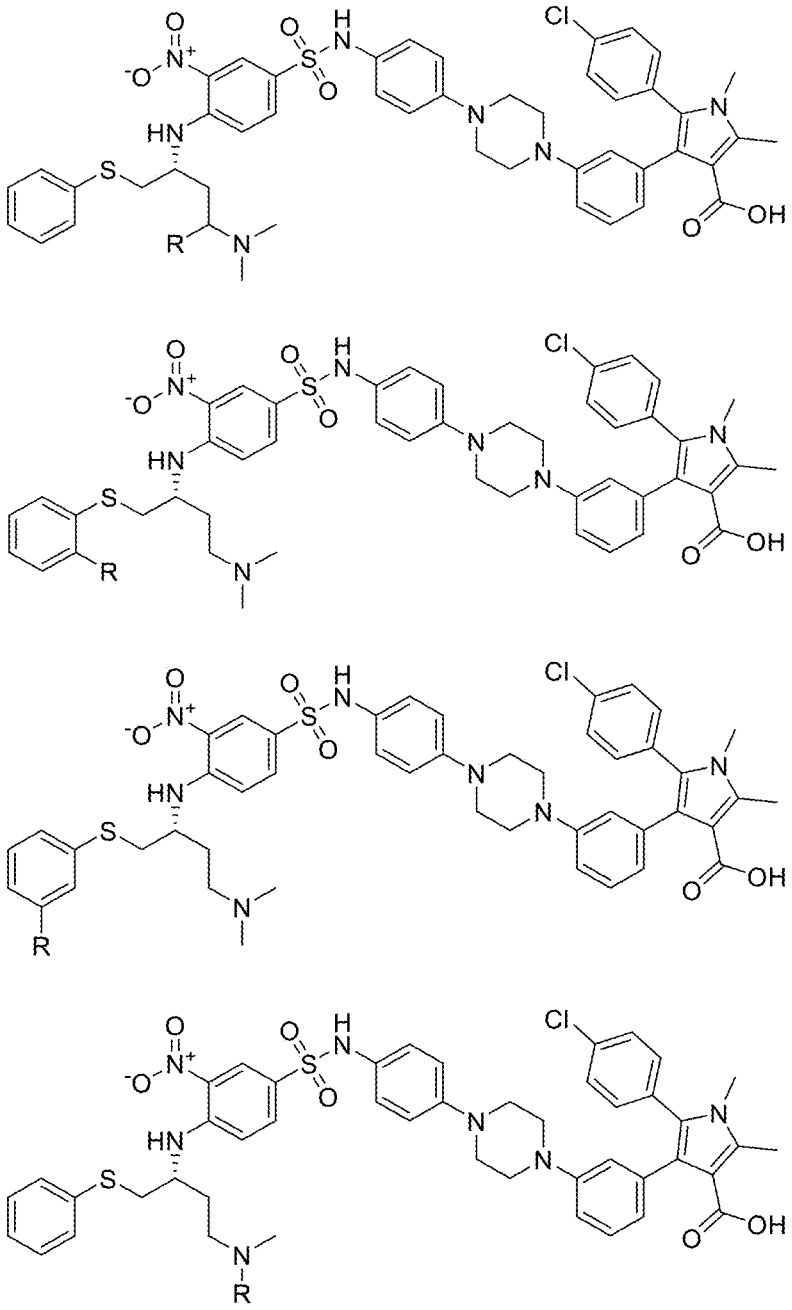


FIG. 2QQ

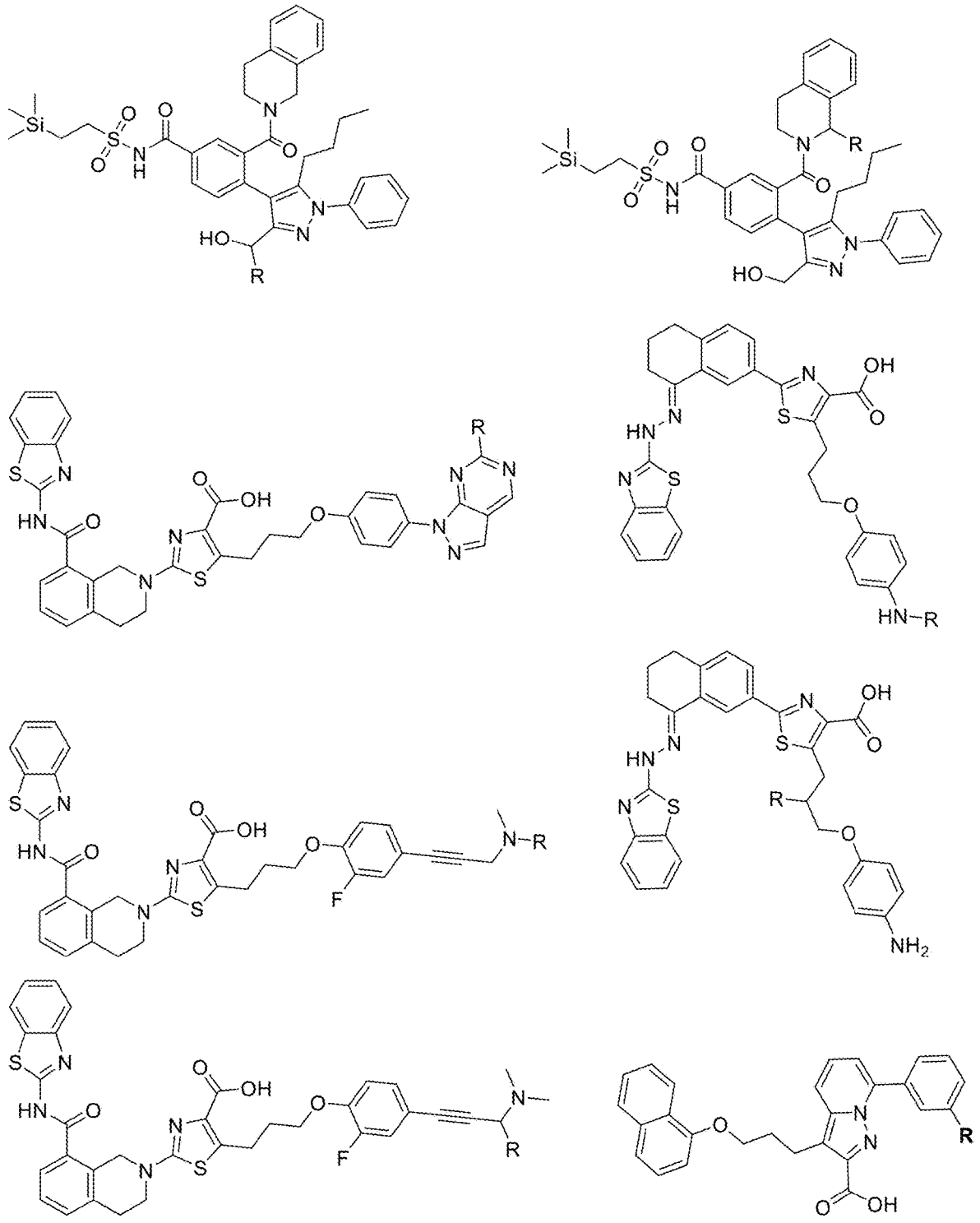
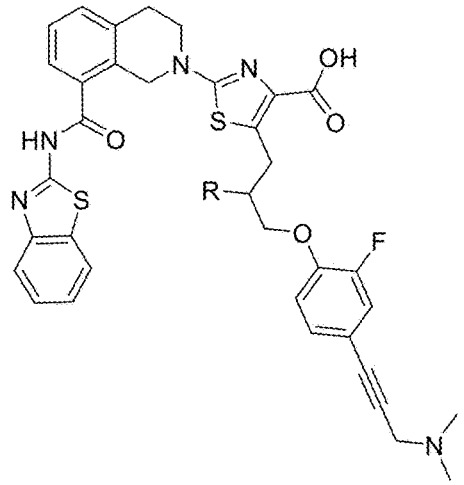
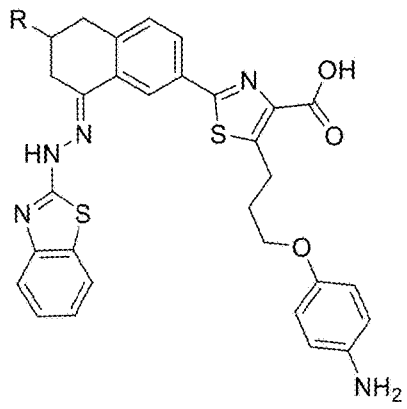
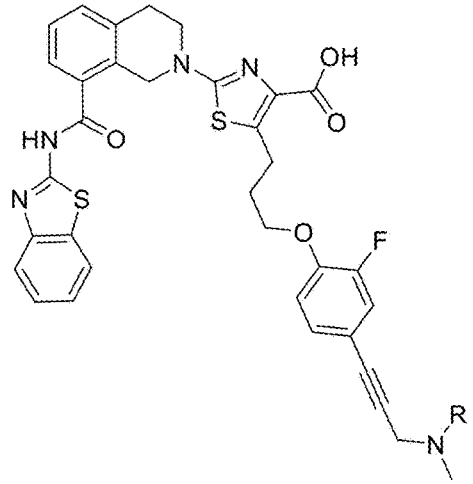
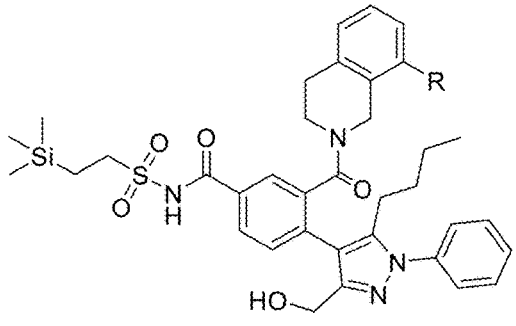


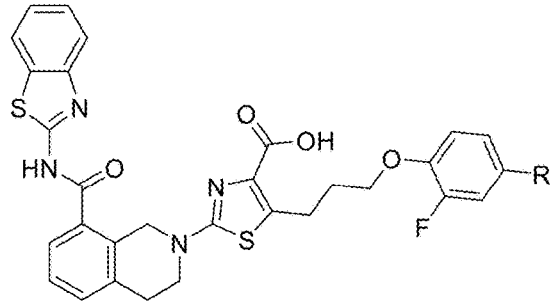
FIG. 2RR











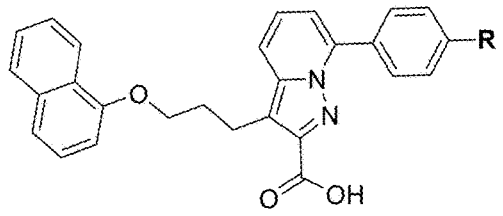


FIG. 2SS

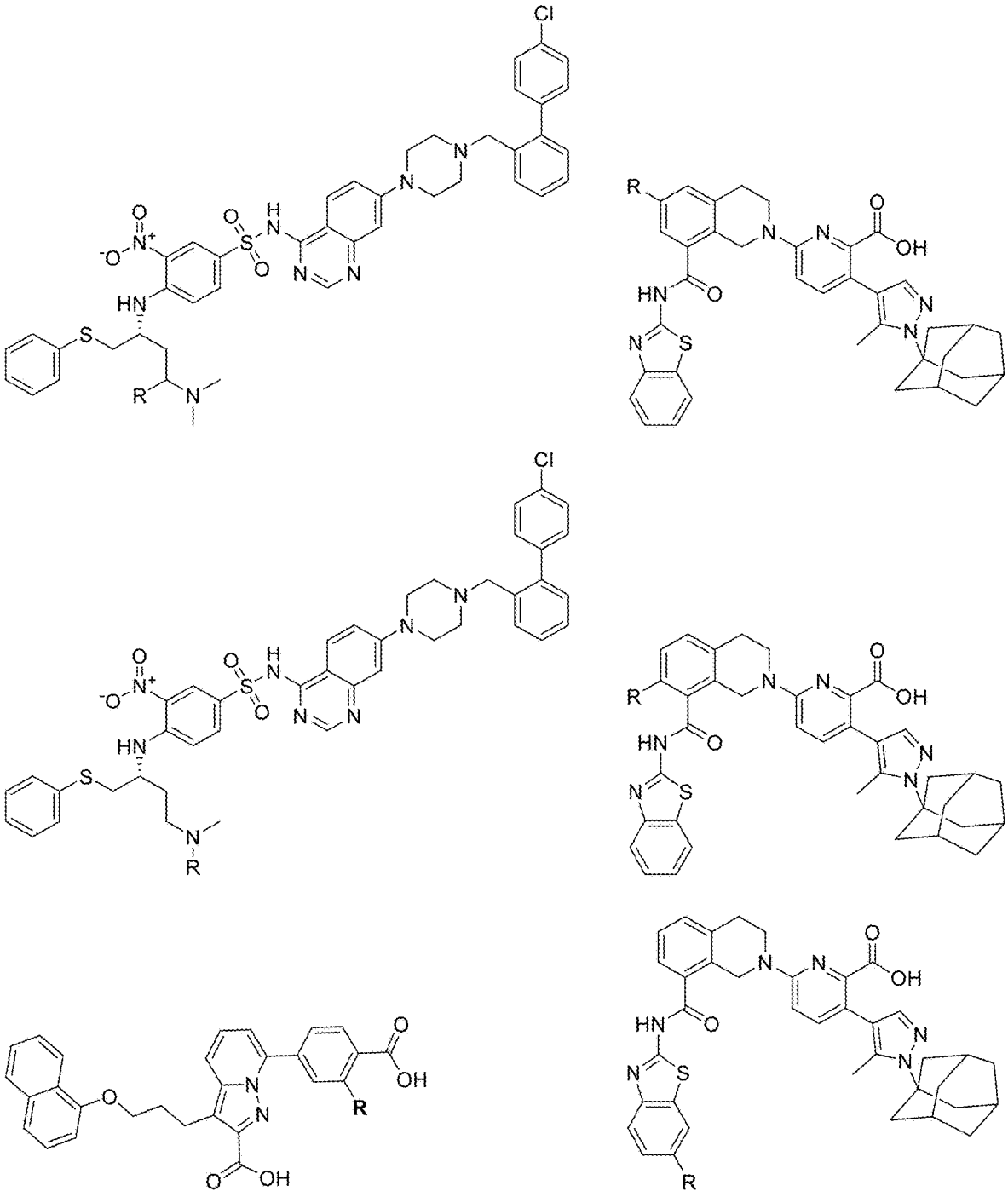


FIG. 2TT

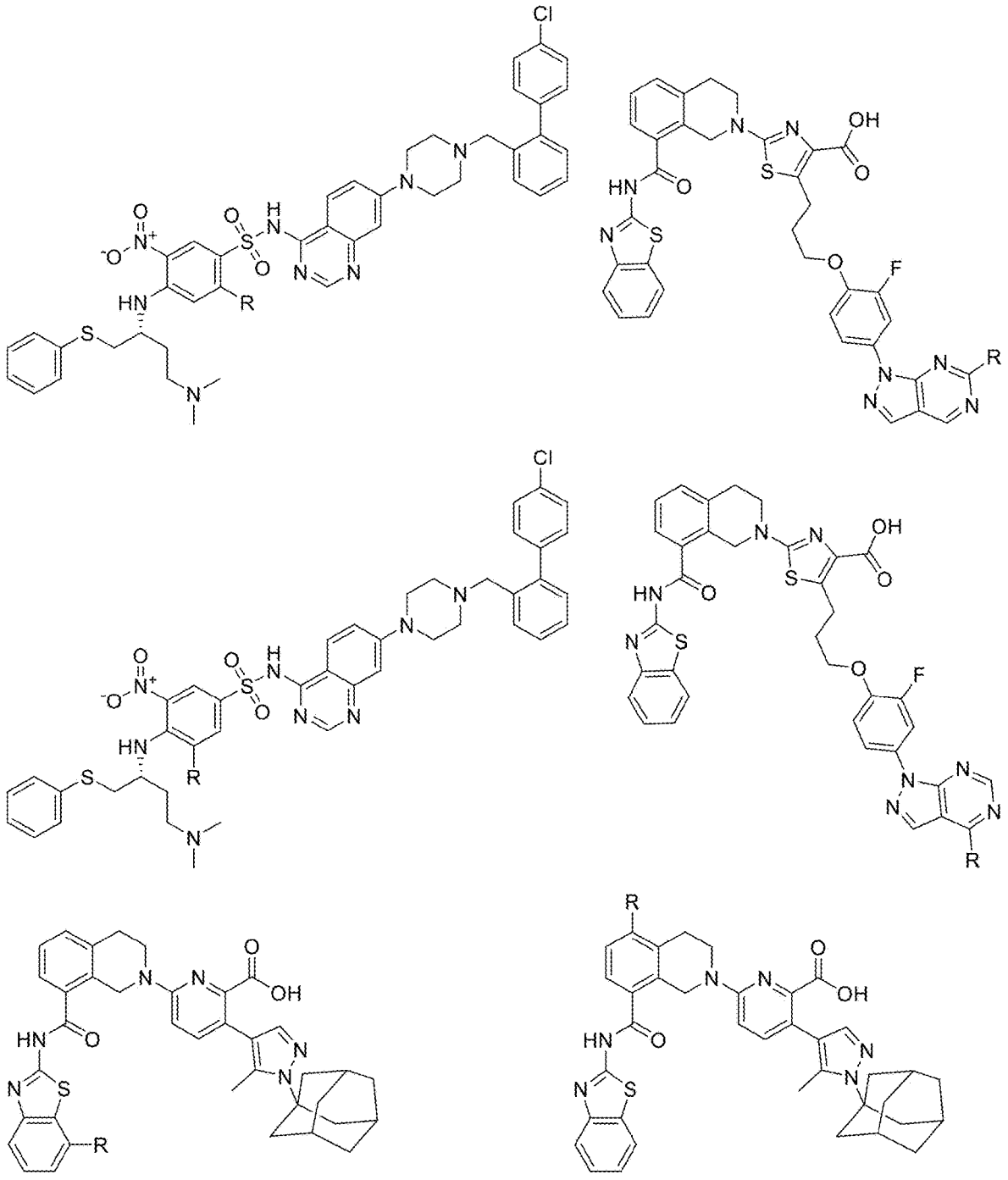


FIG. 2UU

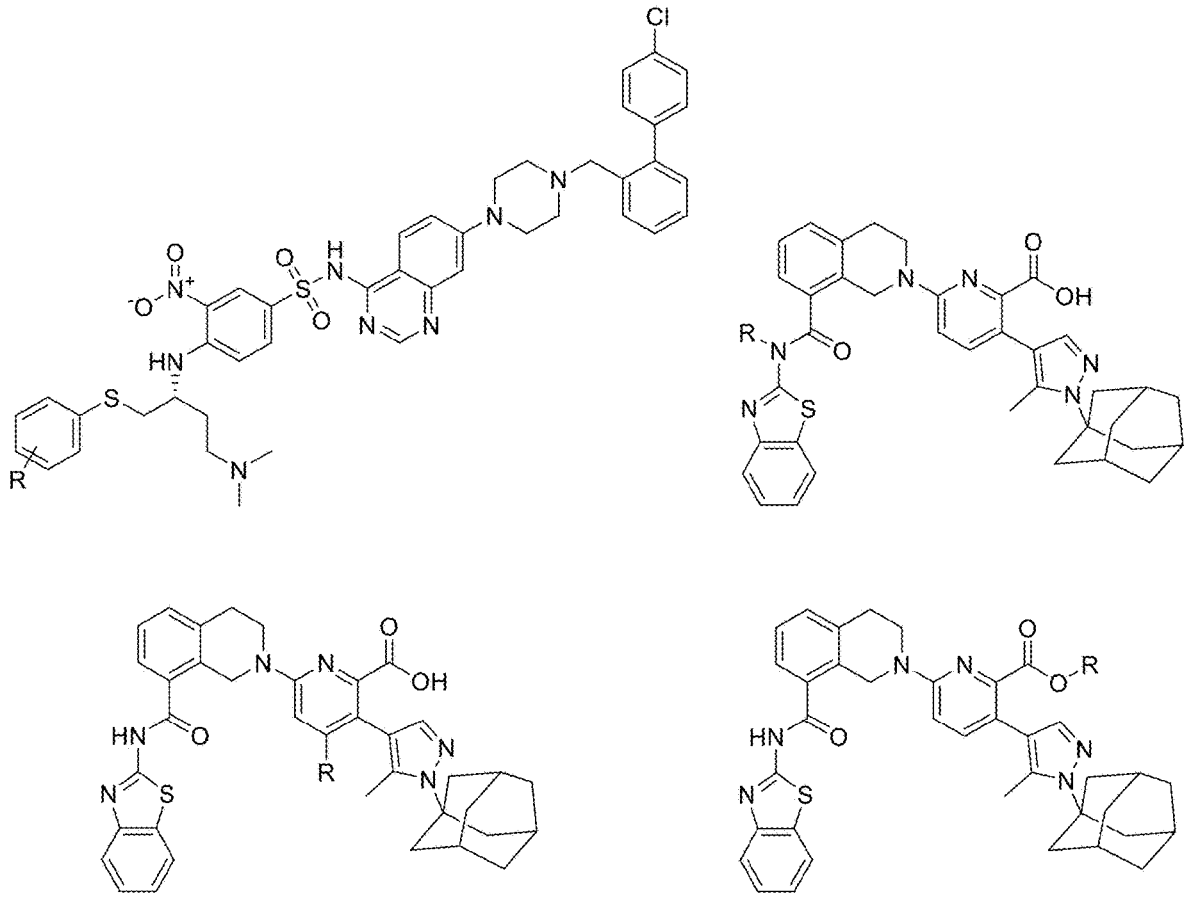


FIG. 2VV

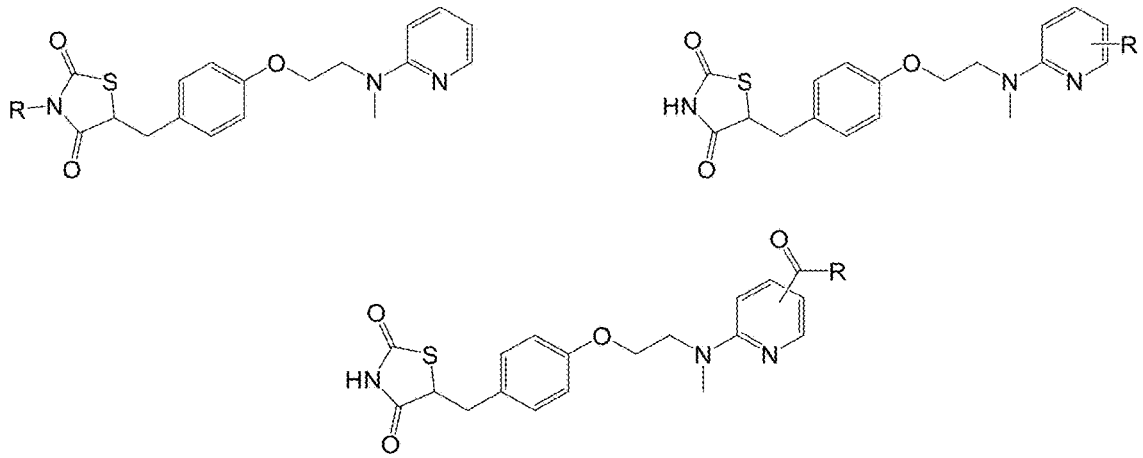


FIG. 2WW

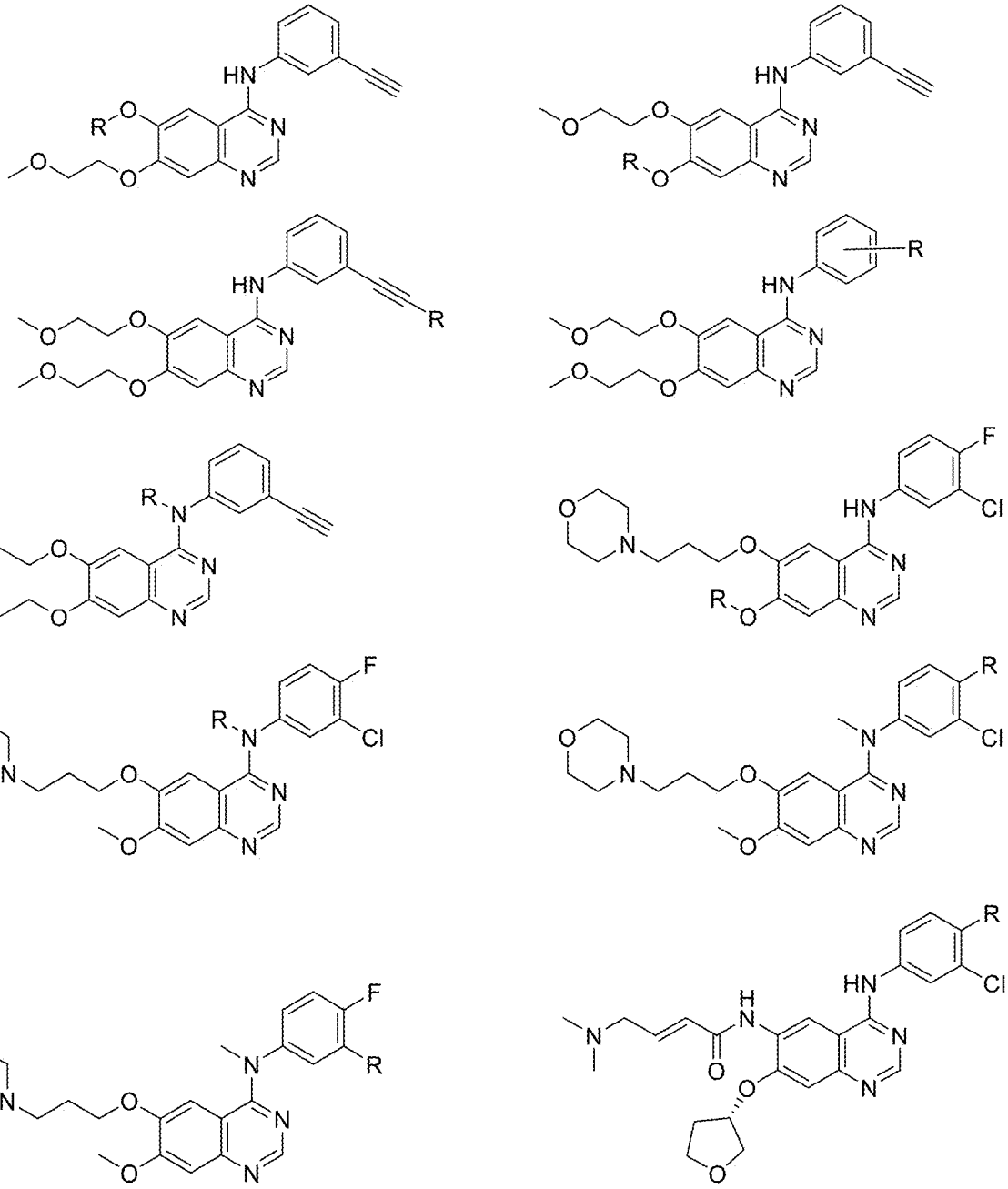
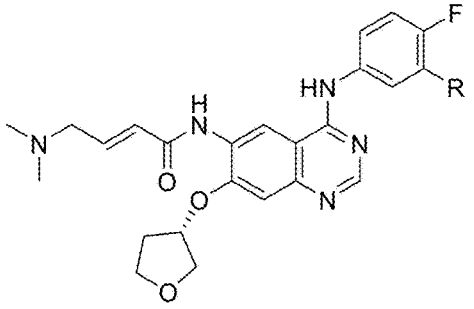
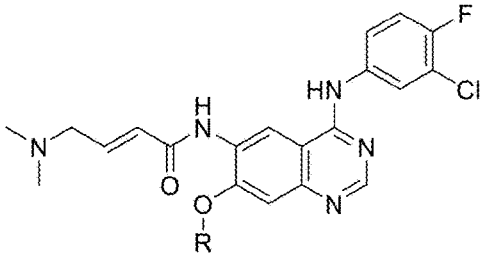
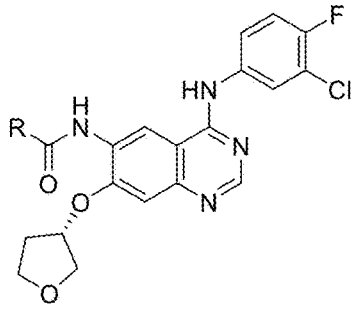
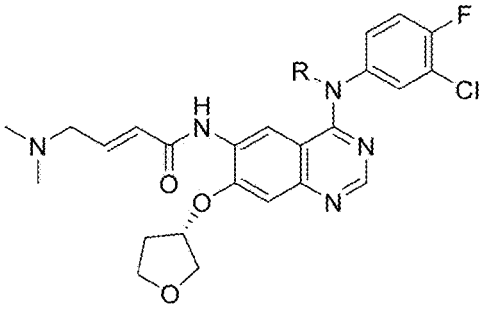


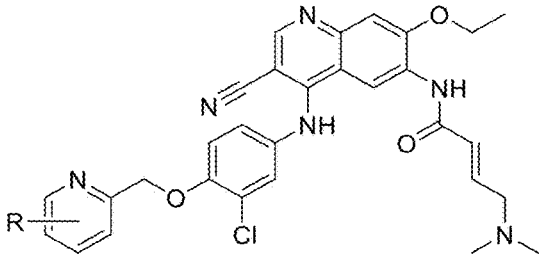
FIG. 2XX

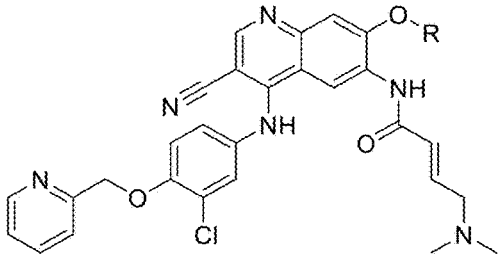


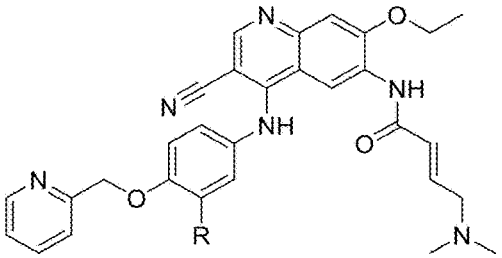












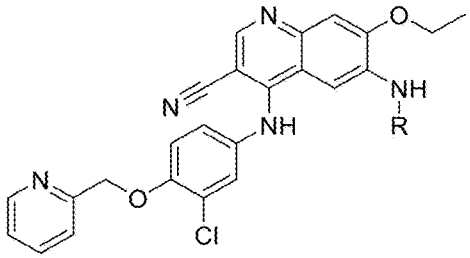


FIG. 2YY

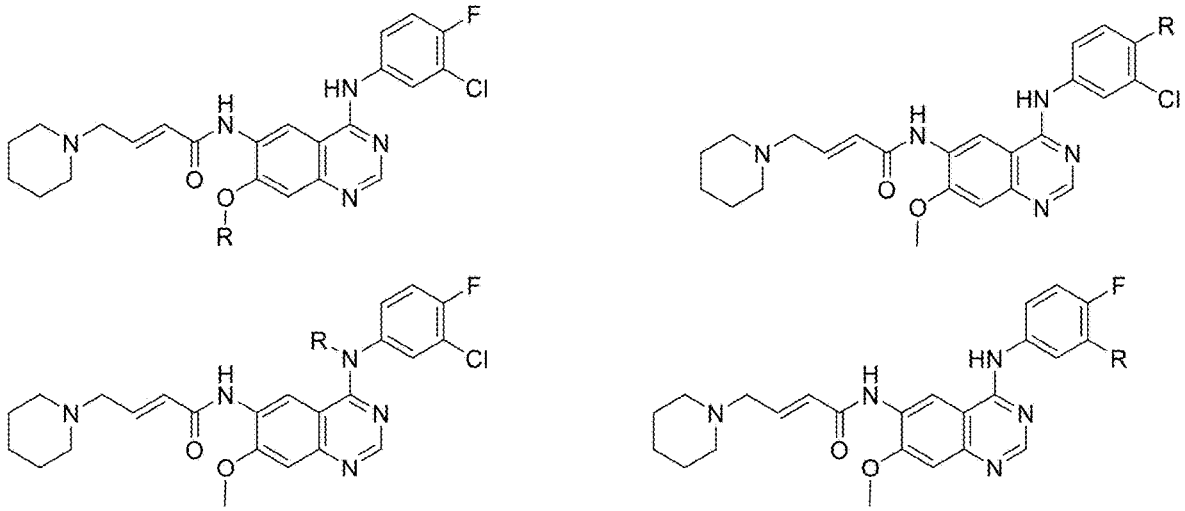


FIG. 2ZZ

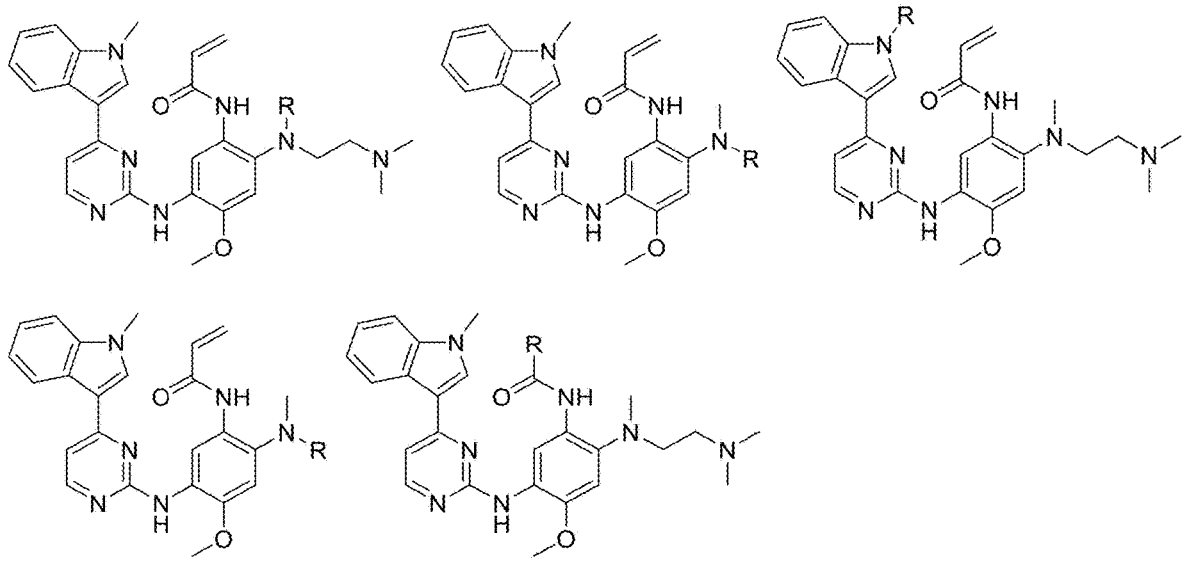


FIG. 2AAA

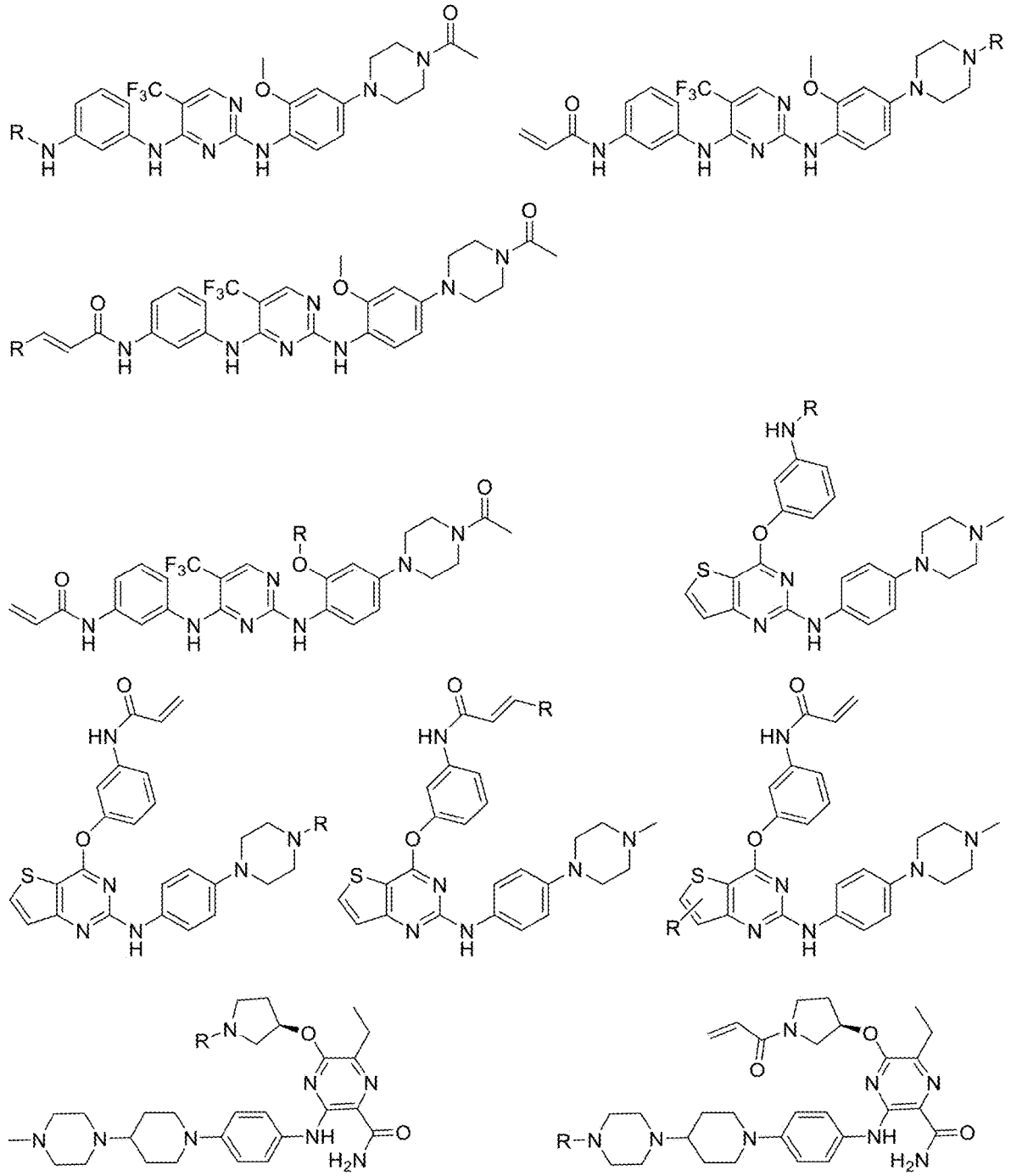


FIG. 2BBB

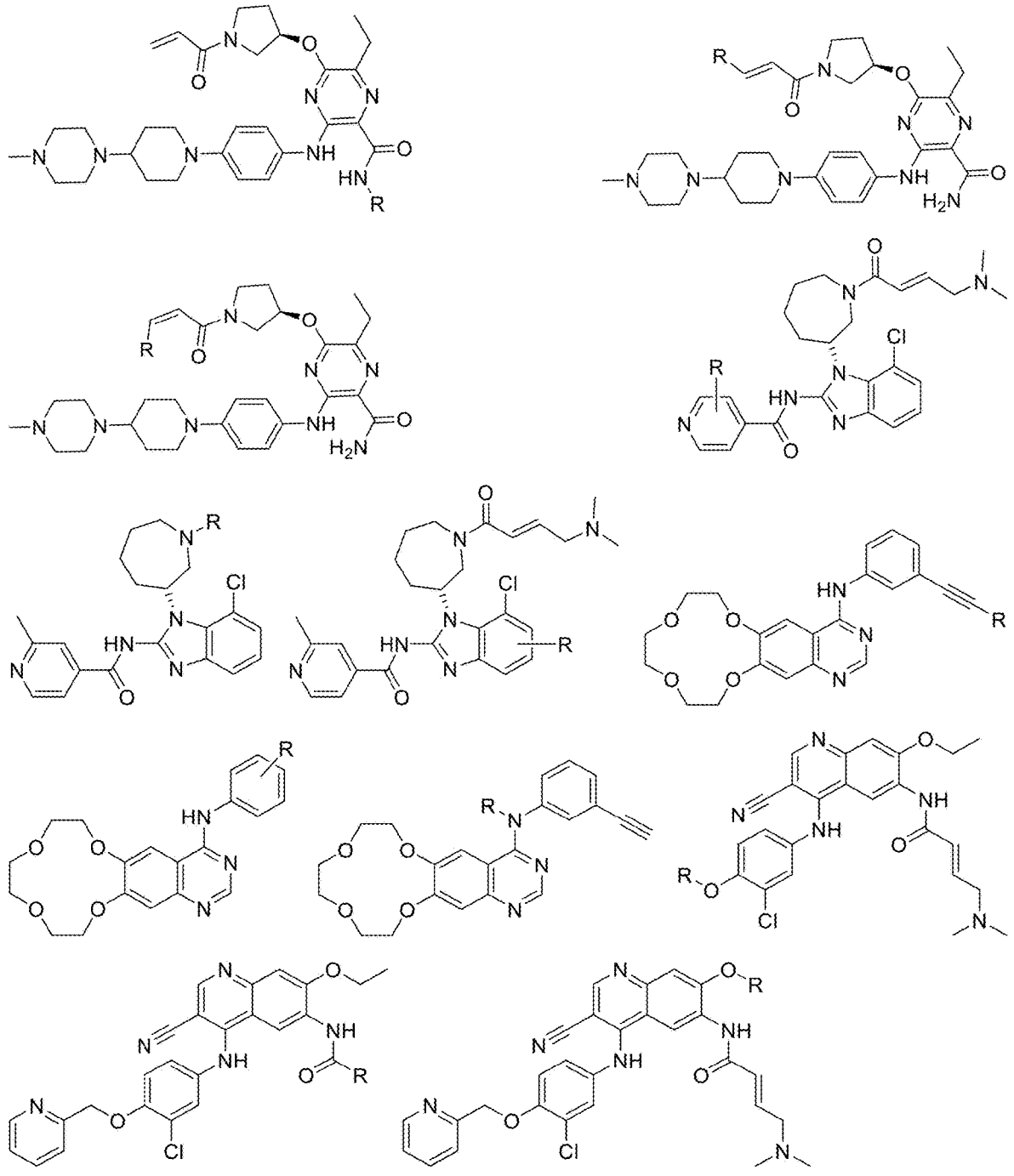


FIG. 2CCC

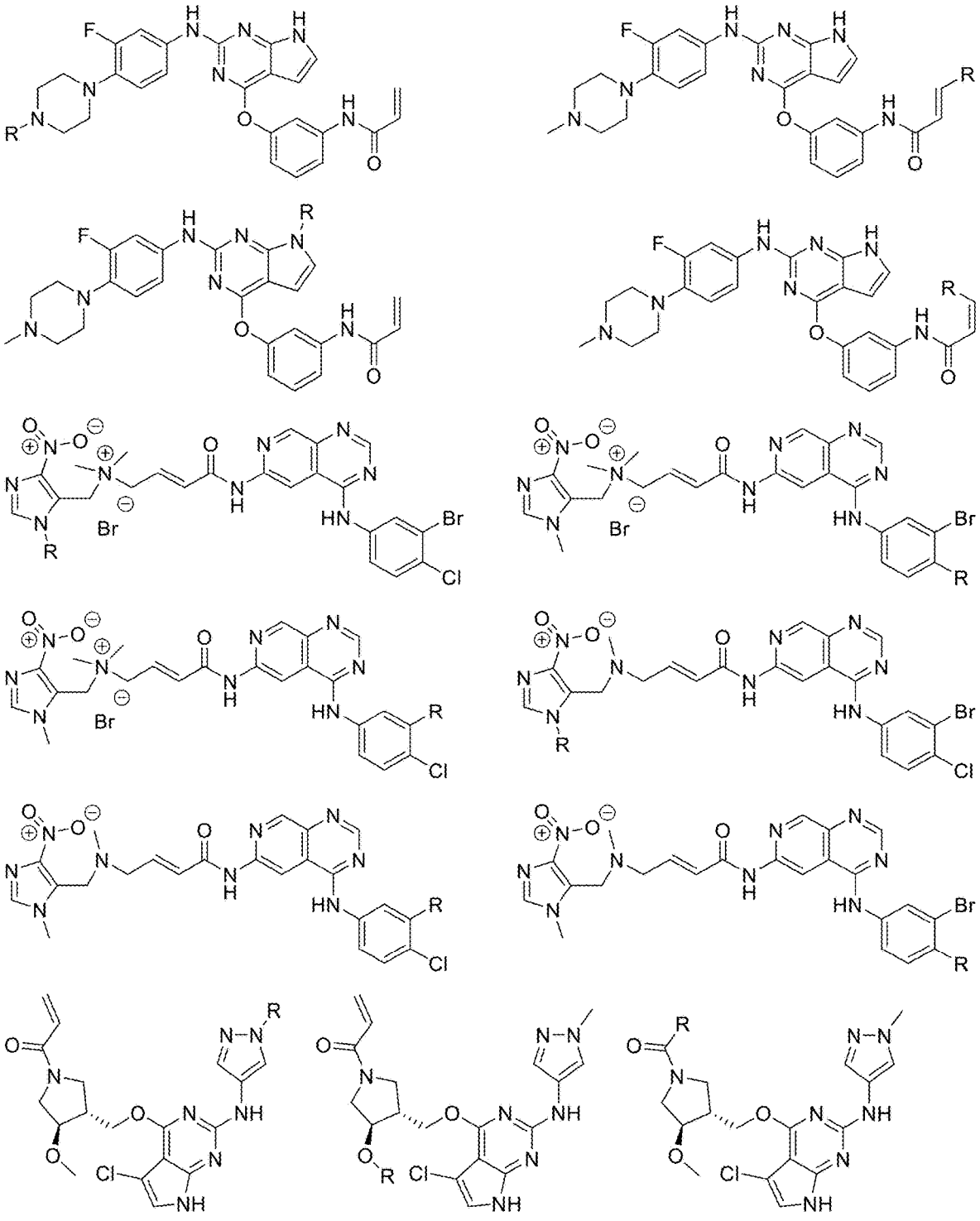


FIG. 2DDD

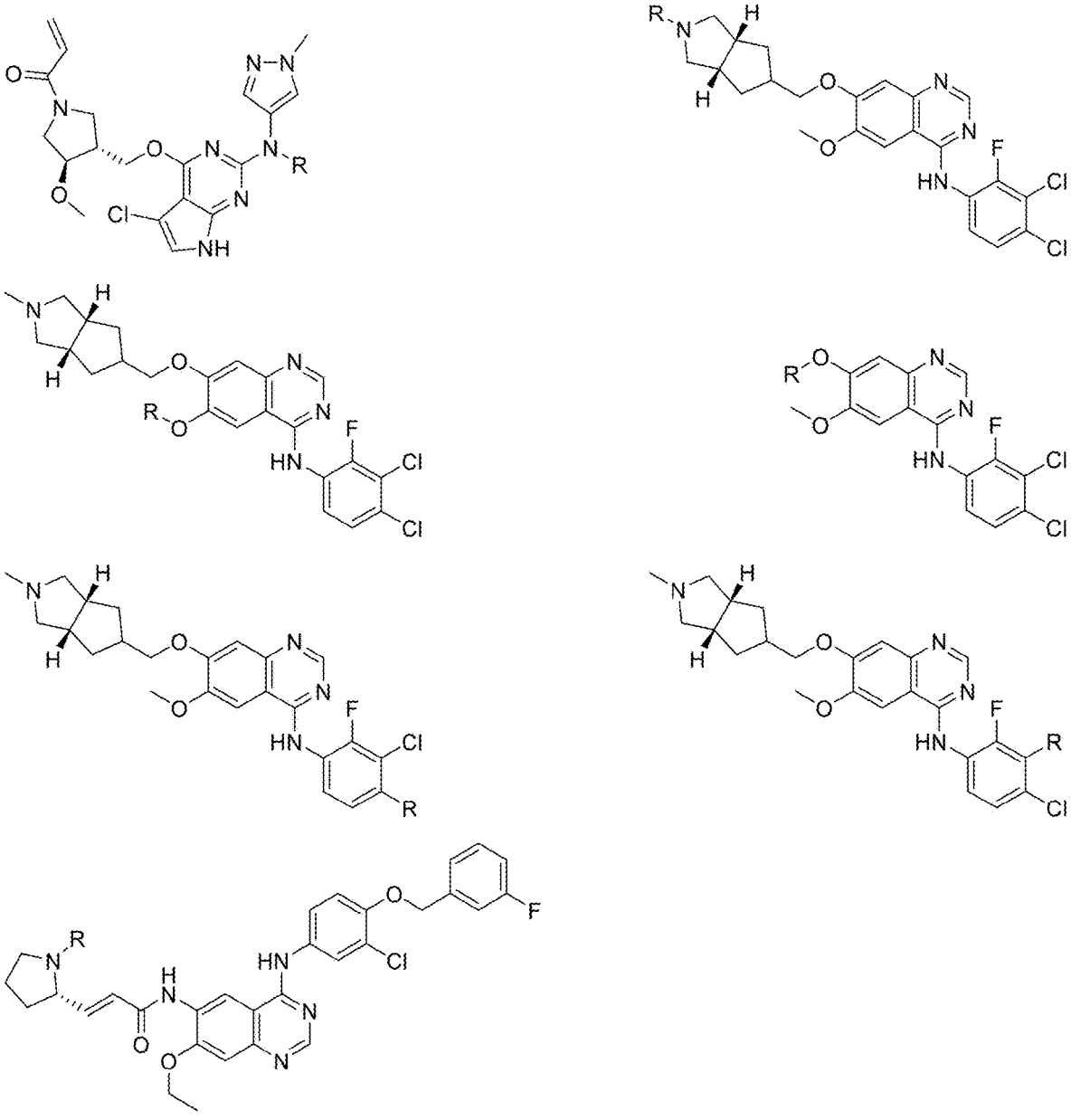
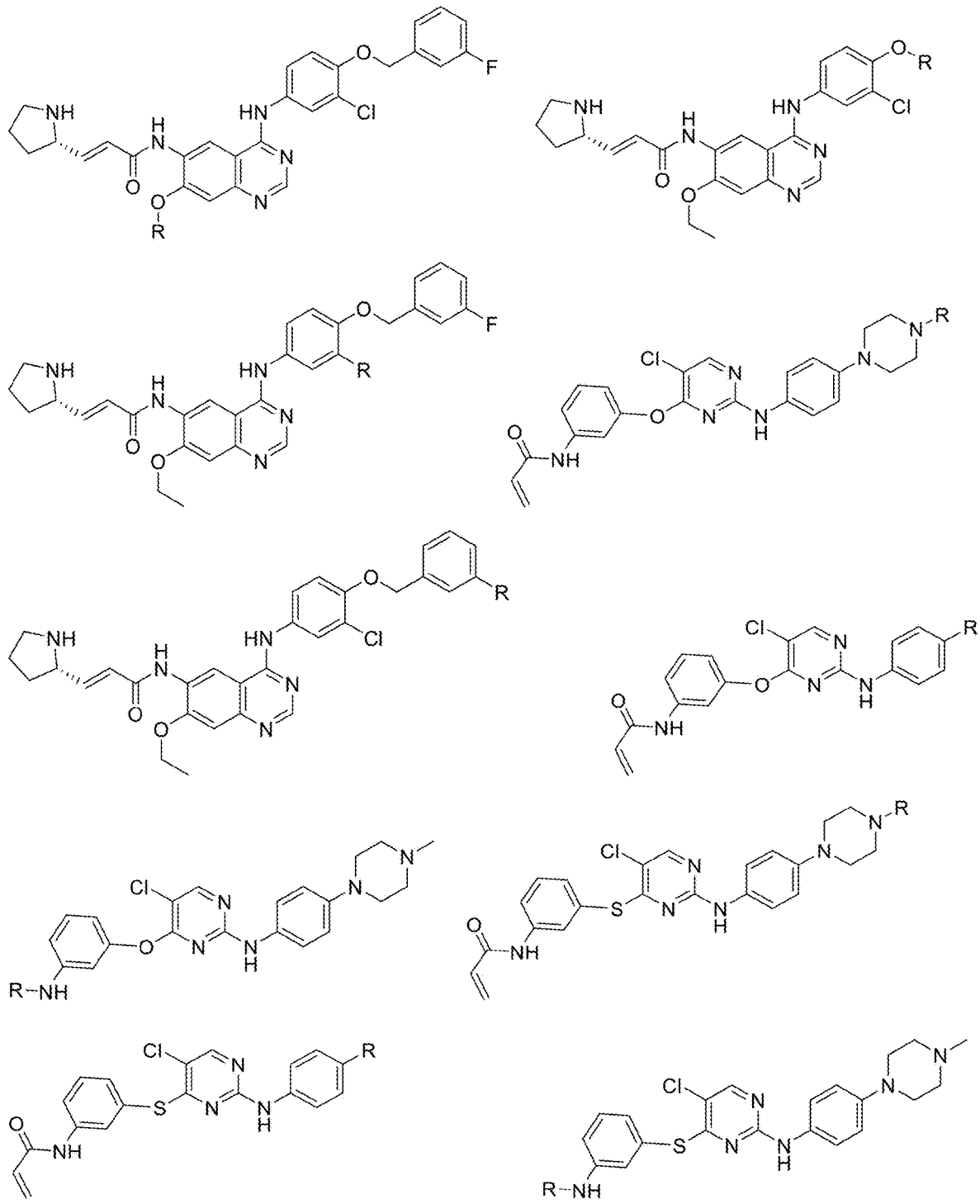


FIG. 2EEE



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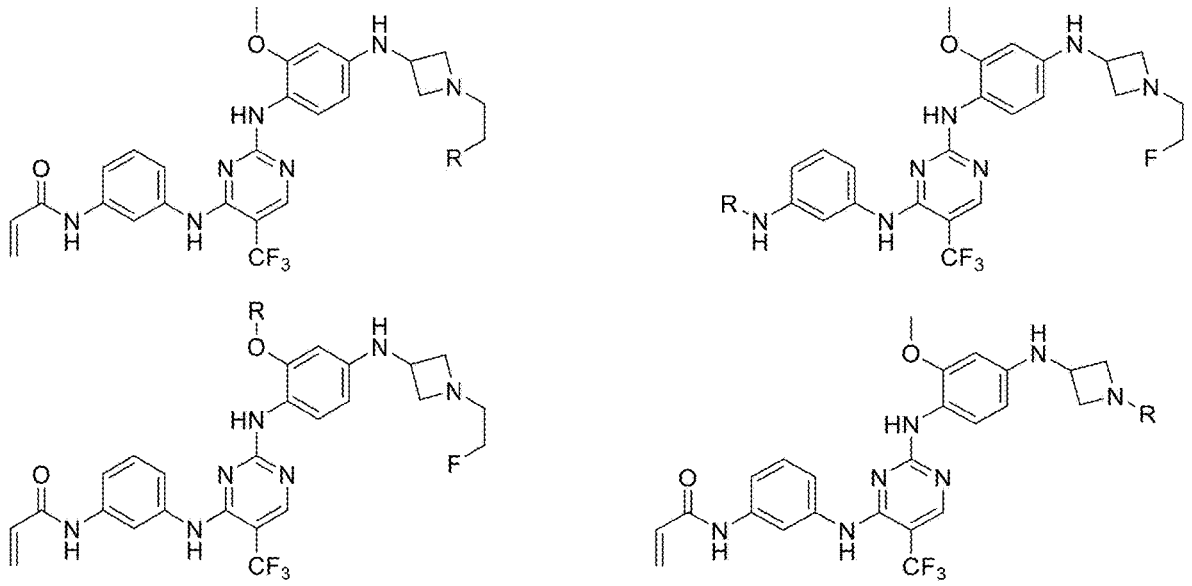


FIG. 2GGG

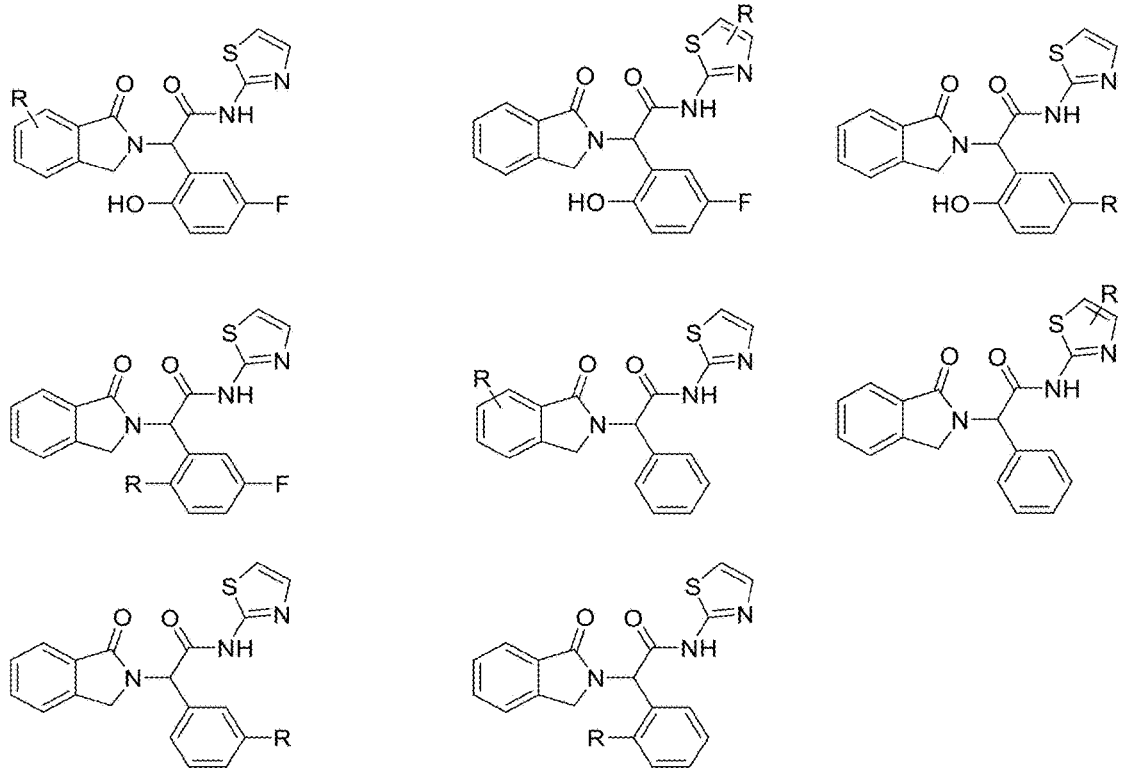


FIG. 2HHH

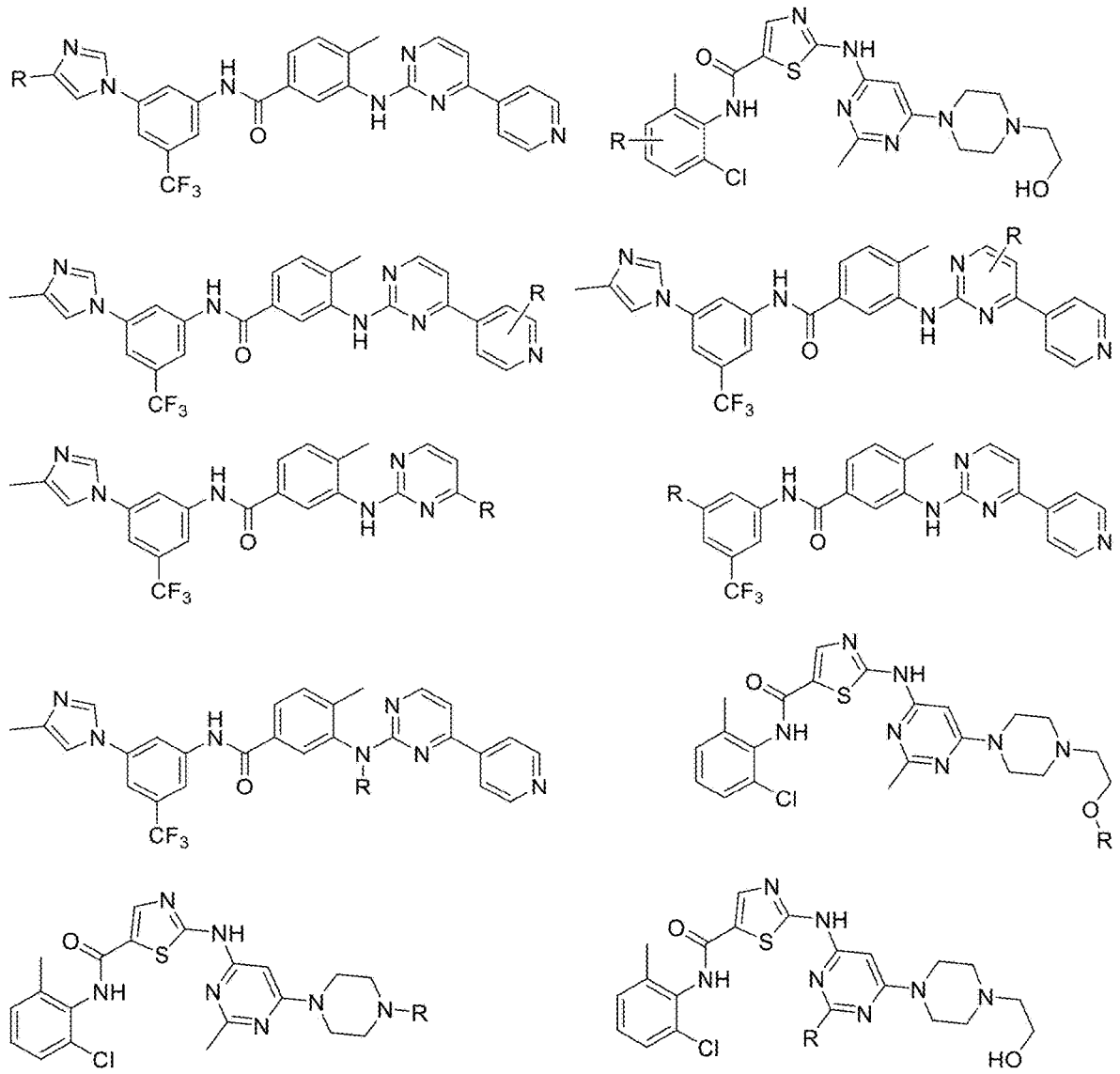


FIG. 2III

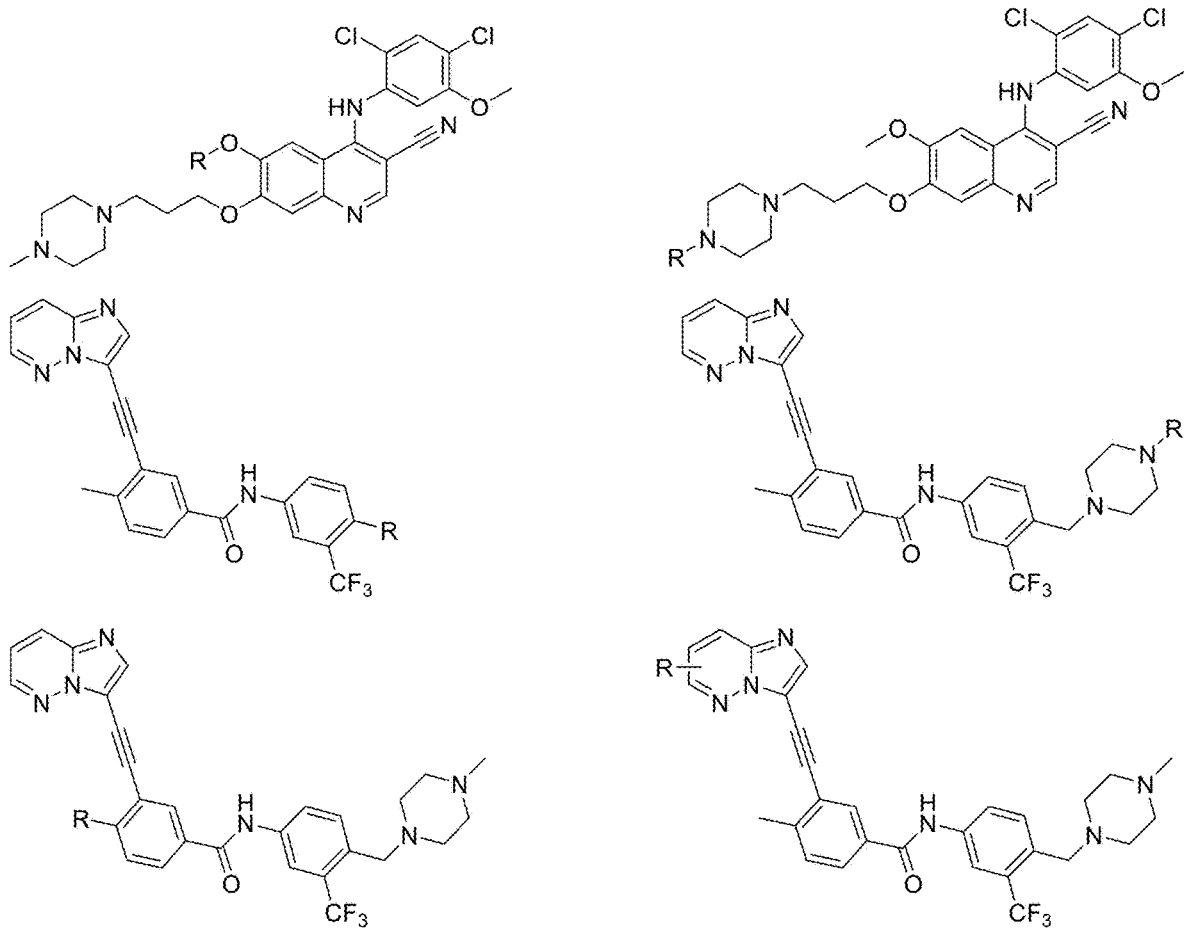


FIG. 2JJJ

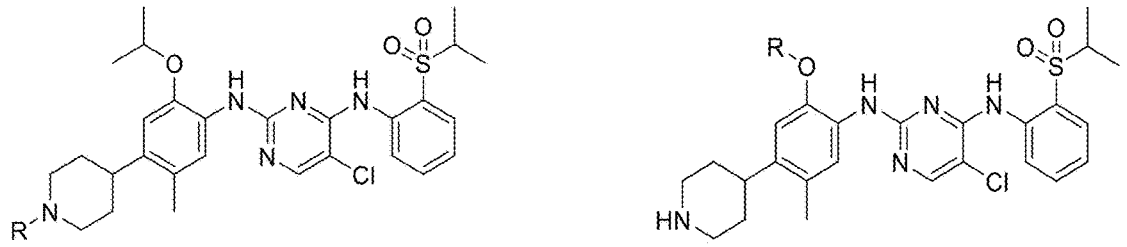


FIG. 2KKK

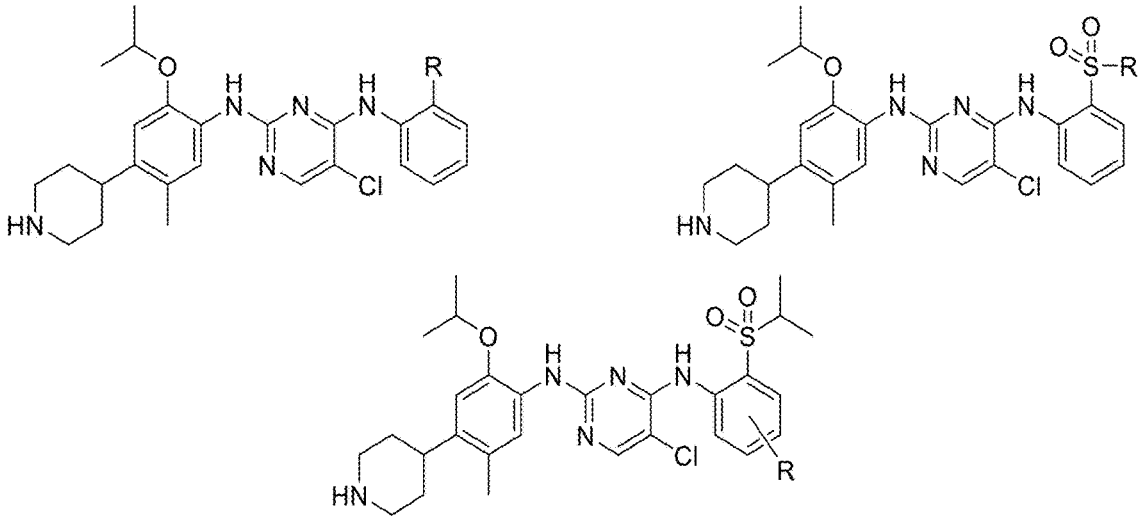


FIG. 2LLL

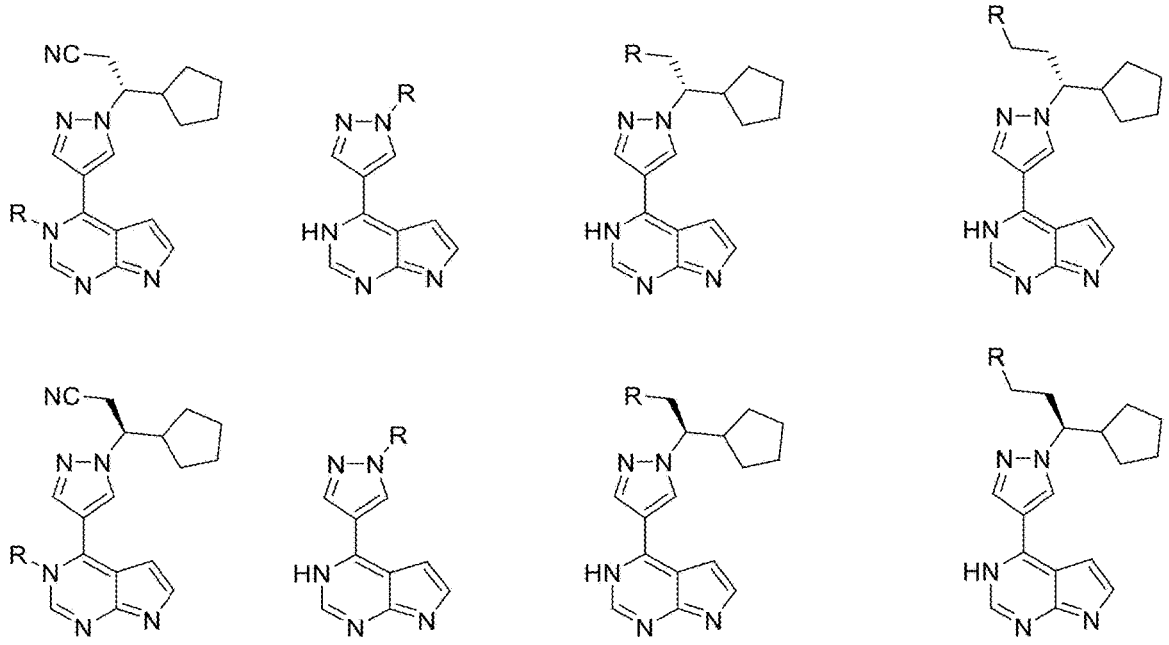


FIG. 2MMM

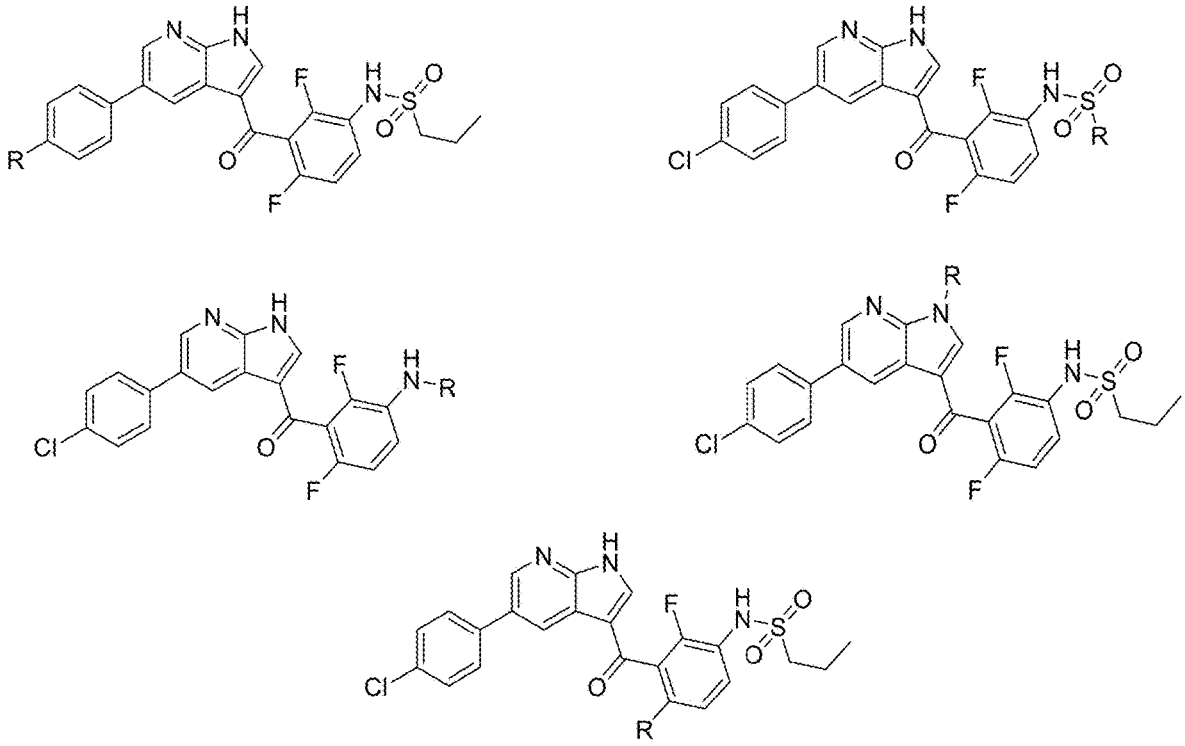


FIG. 2NNN

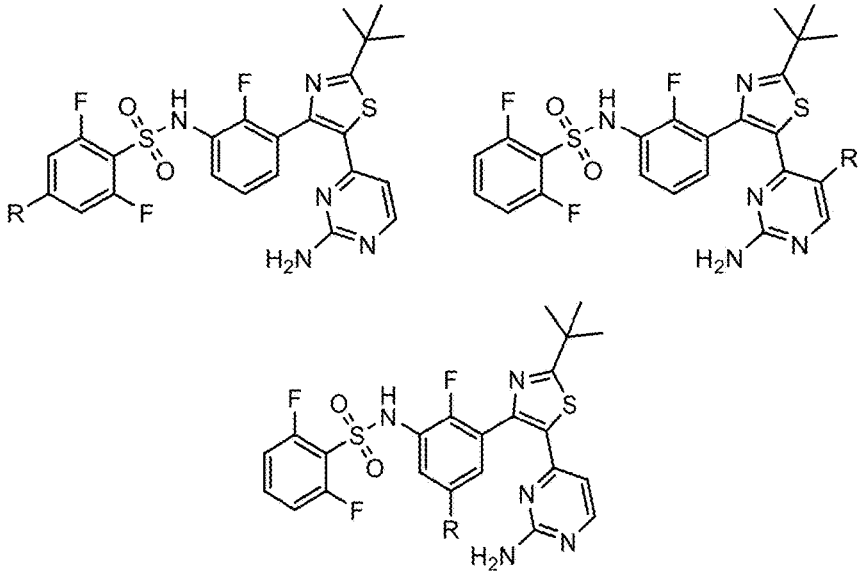


FIG. 2OOO

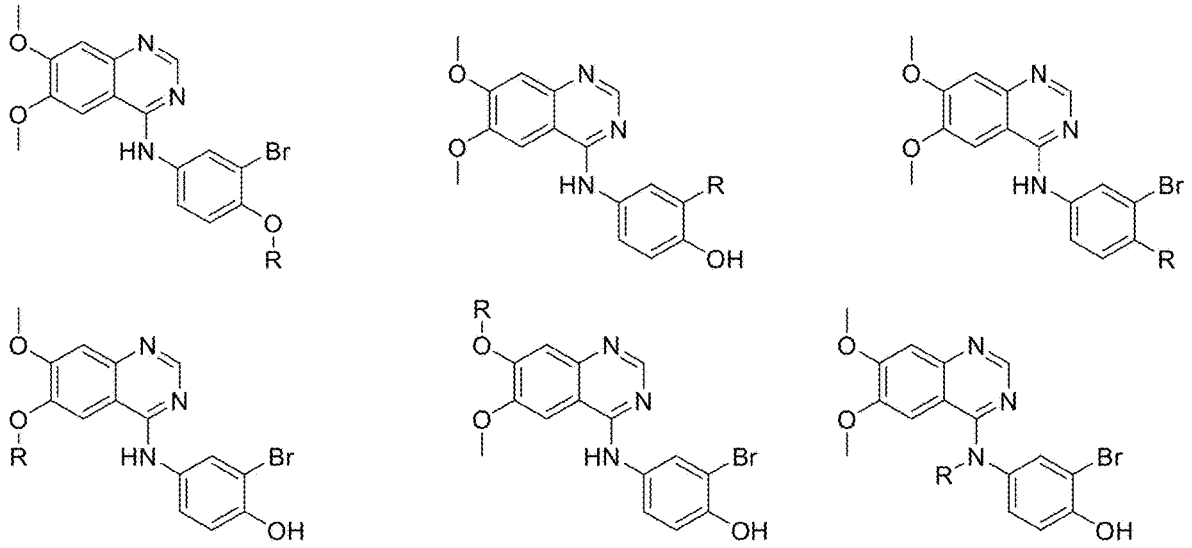


FIG. 2PPP

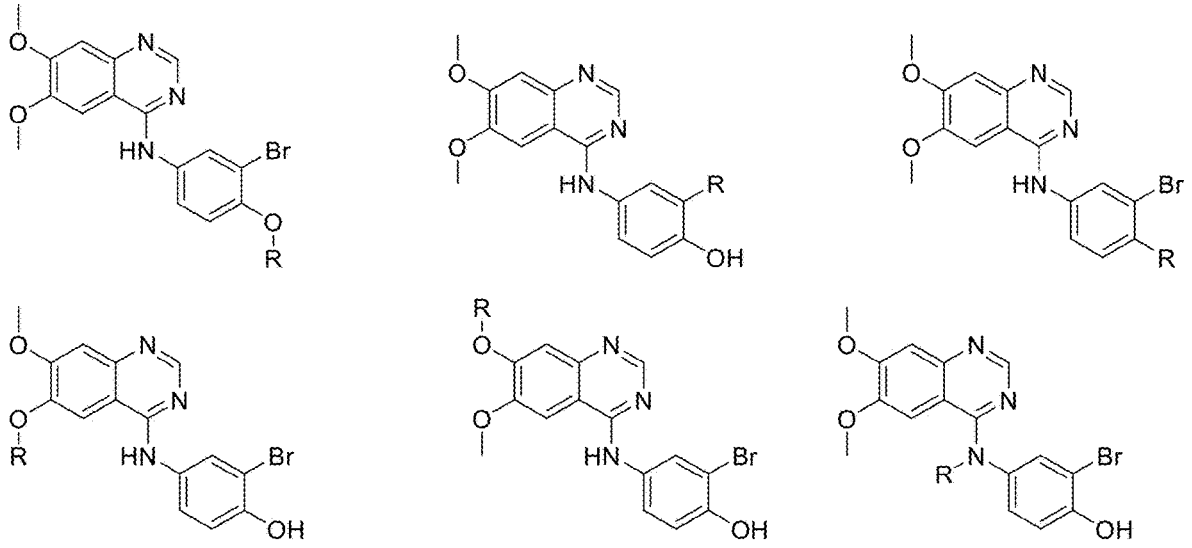


FIG. 2QQQ

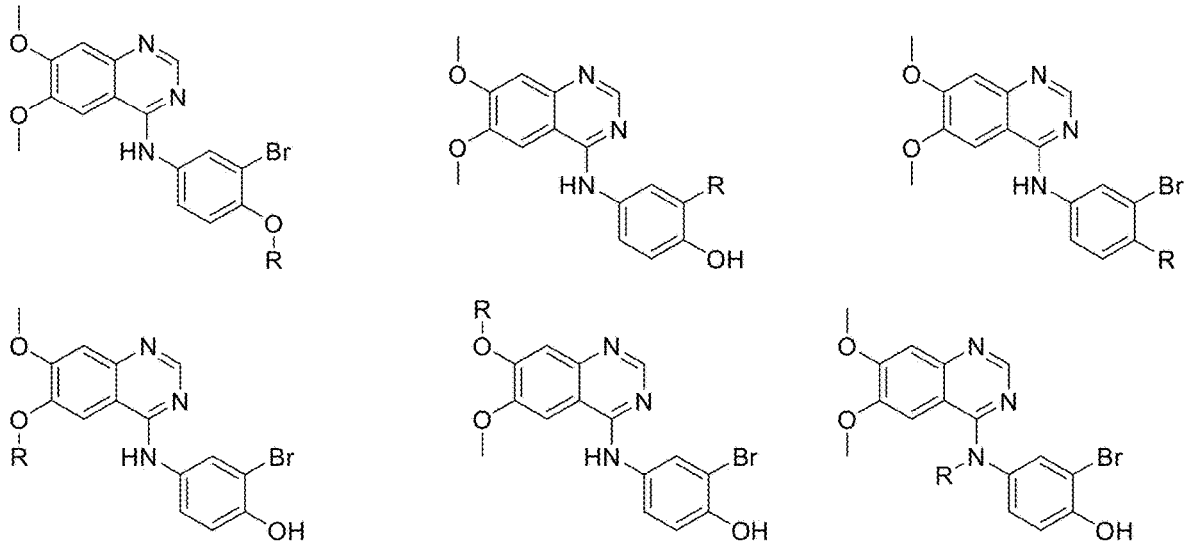


FIG. 2RRR

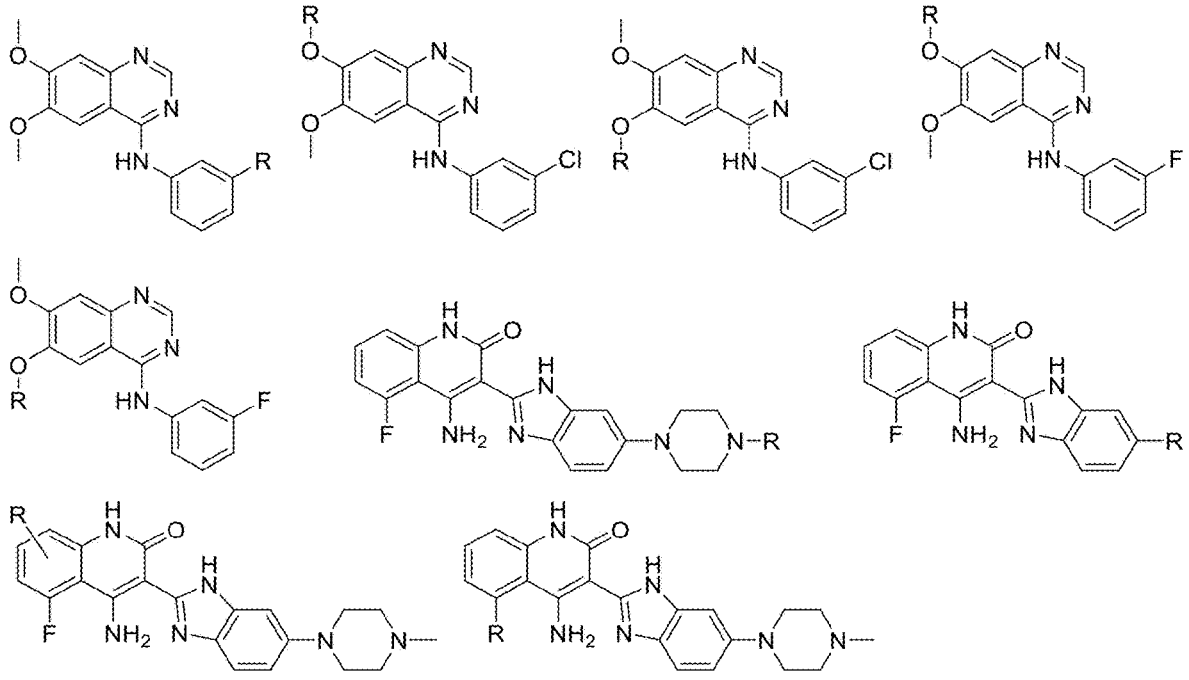


FIG. 2SSS

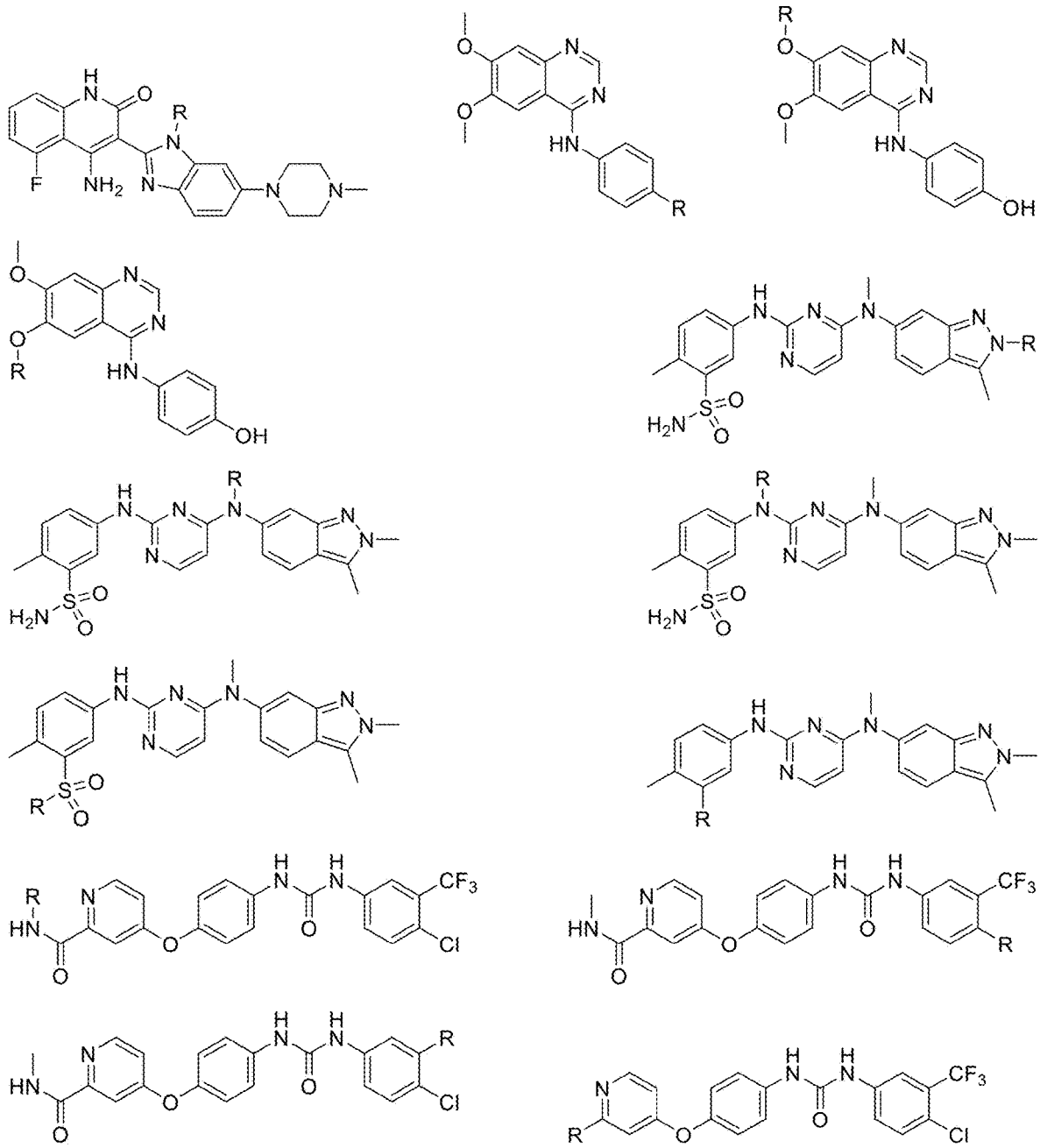


FIG. 2TTT

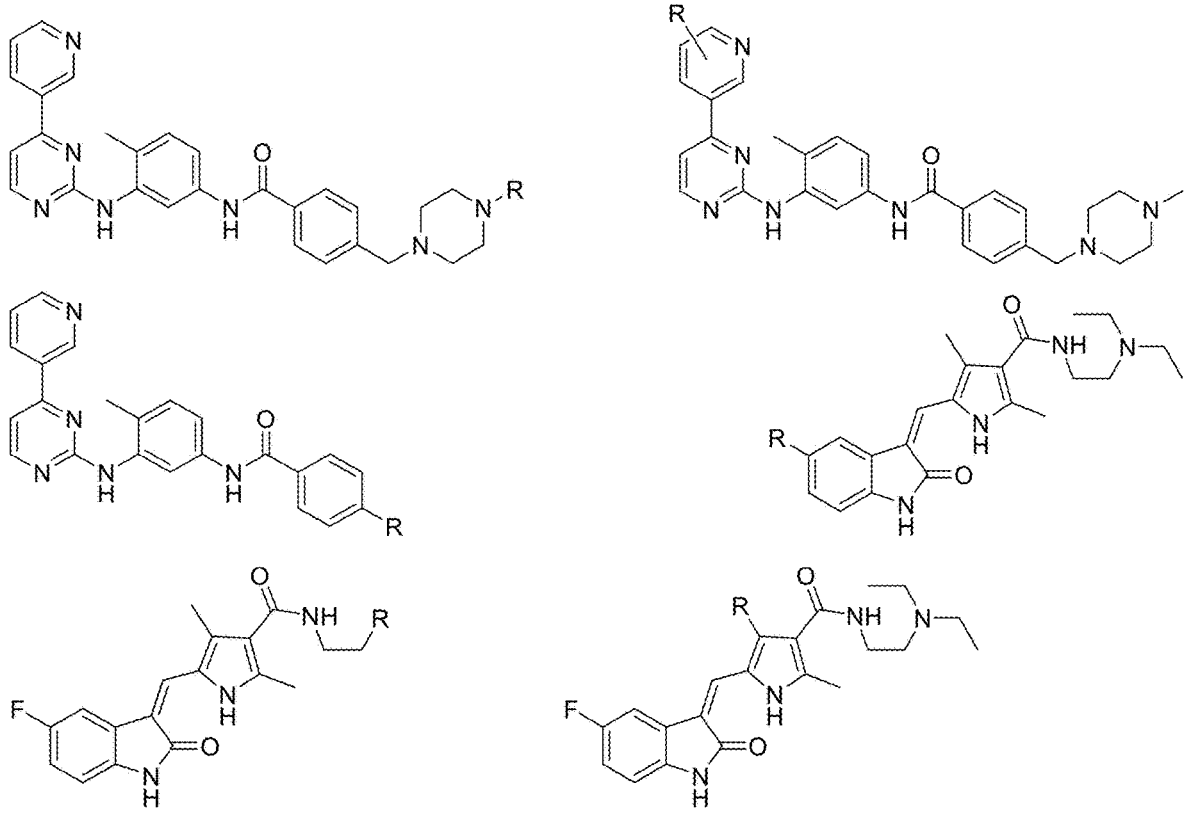


FIG. 2UUU

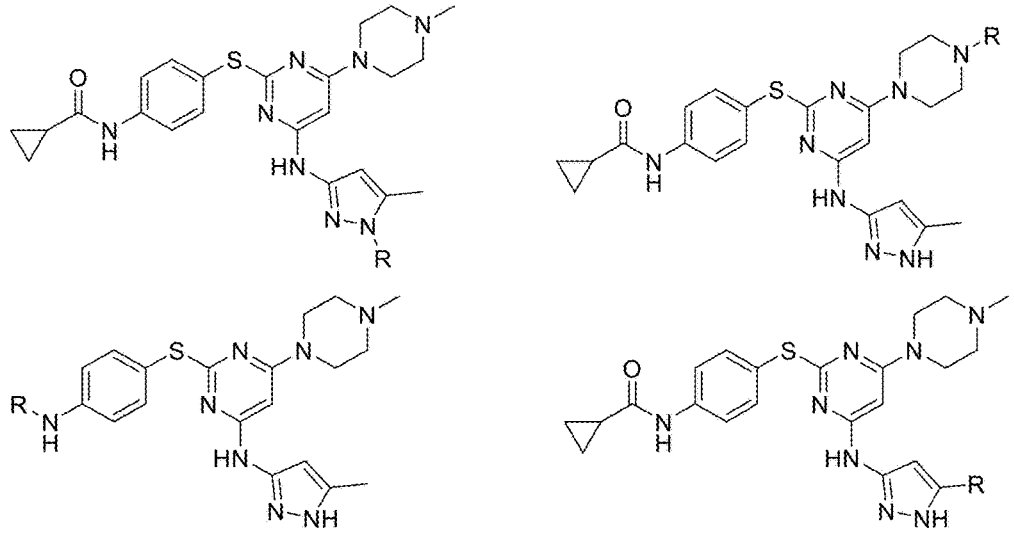


FIG. 2VVV

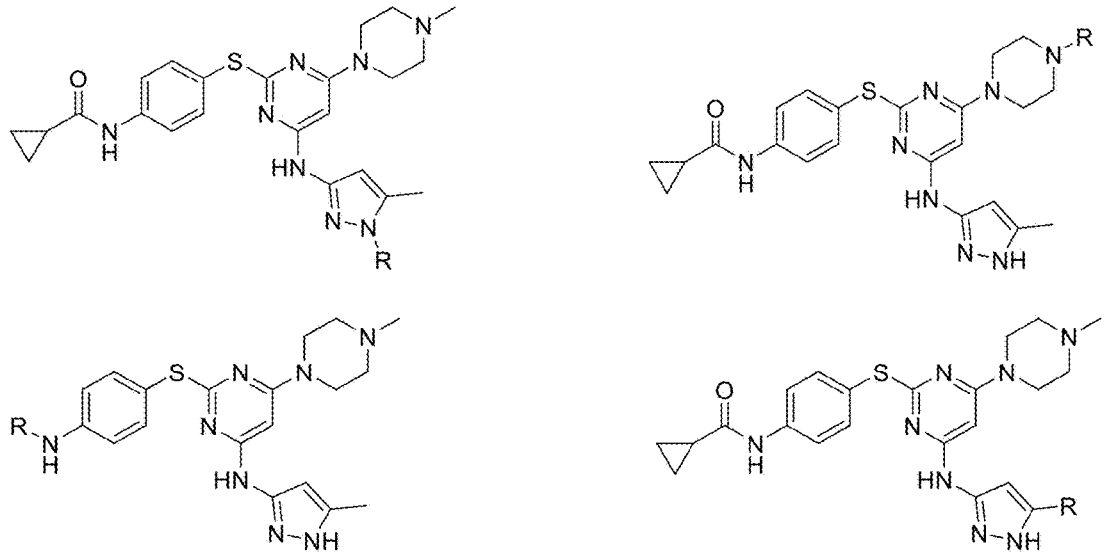


FIG. 2WWW

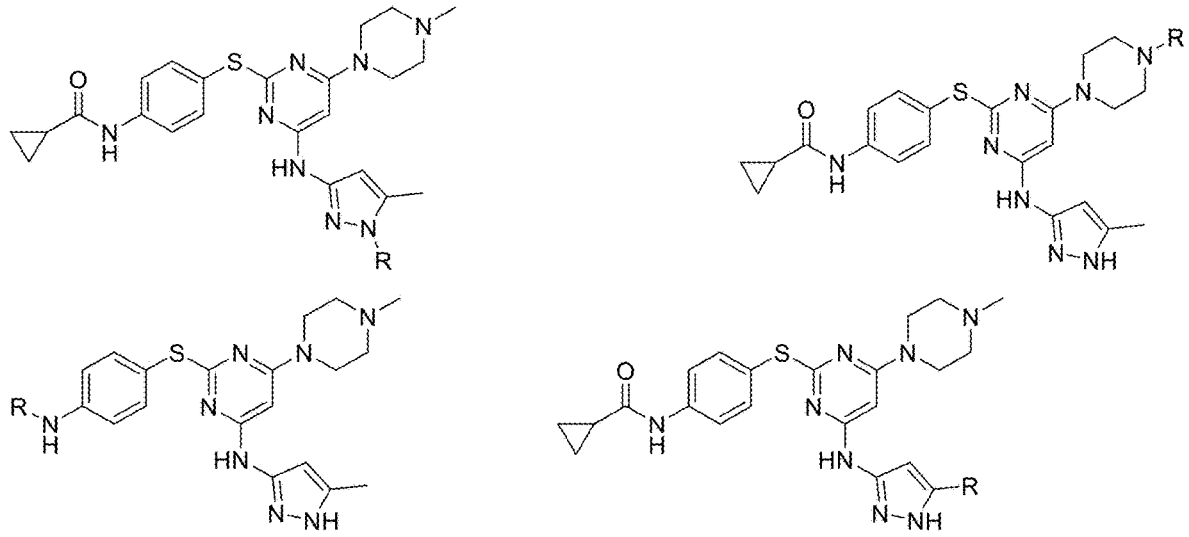


FIG. 2XXX

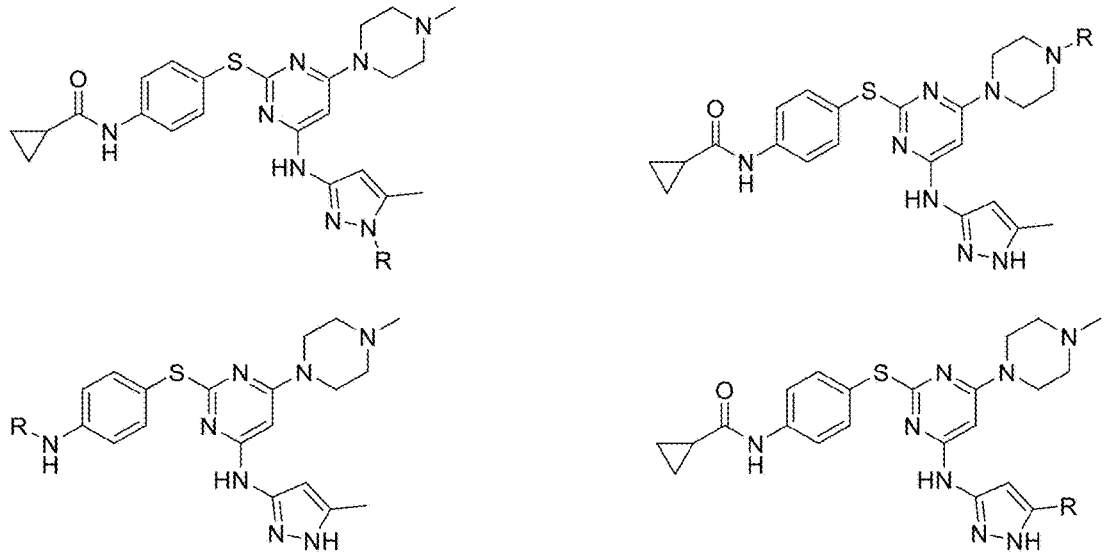


FIG. 2YYY

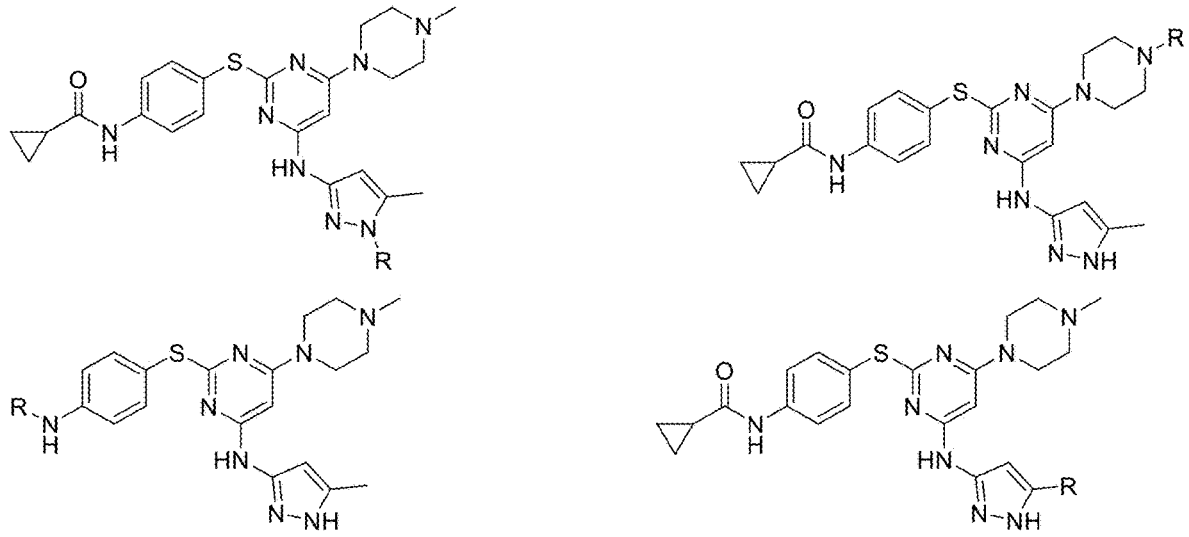


FIG. 2ZZZ

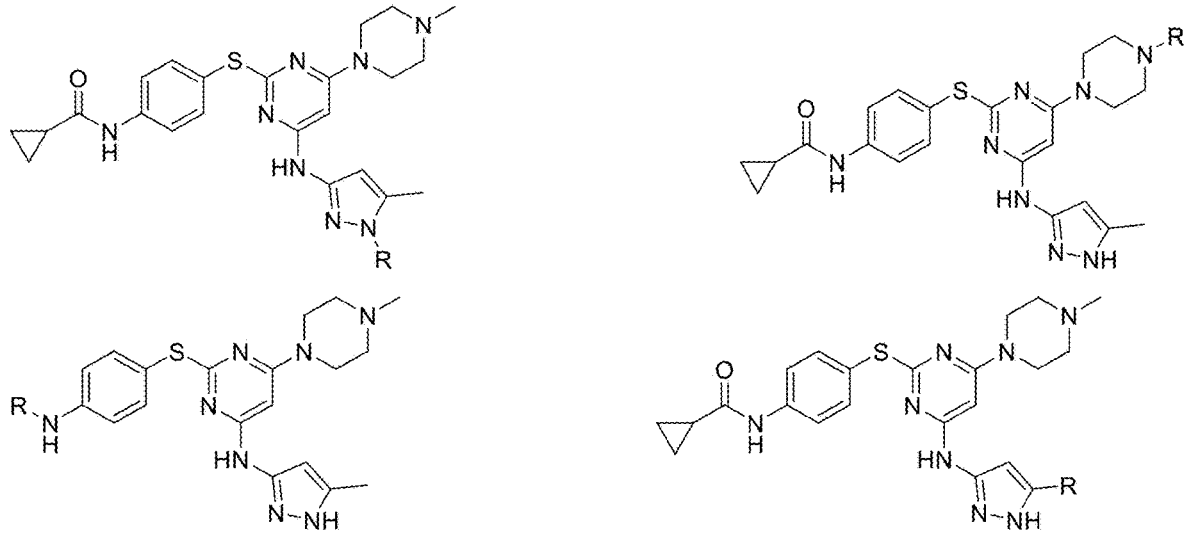


FIG. 2AAAA

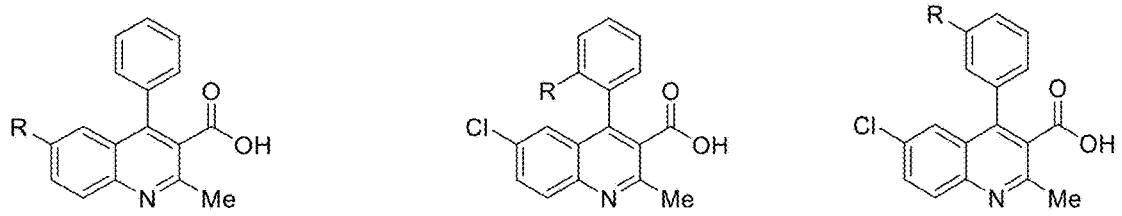


FIG. 2BBBB

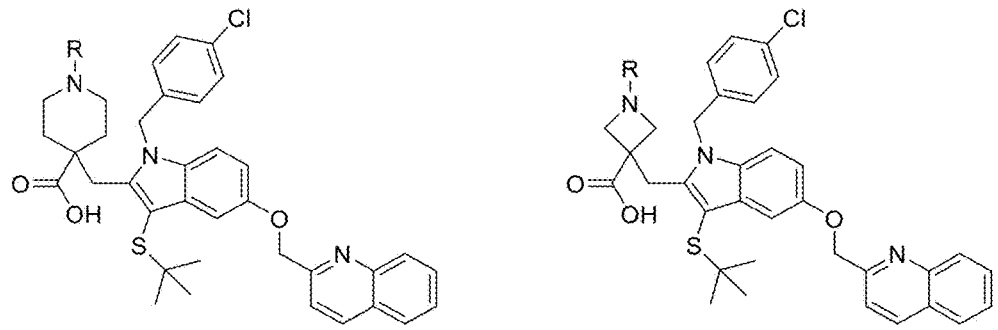


FIG. 2CCCC

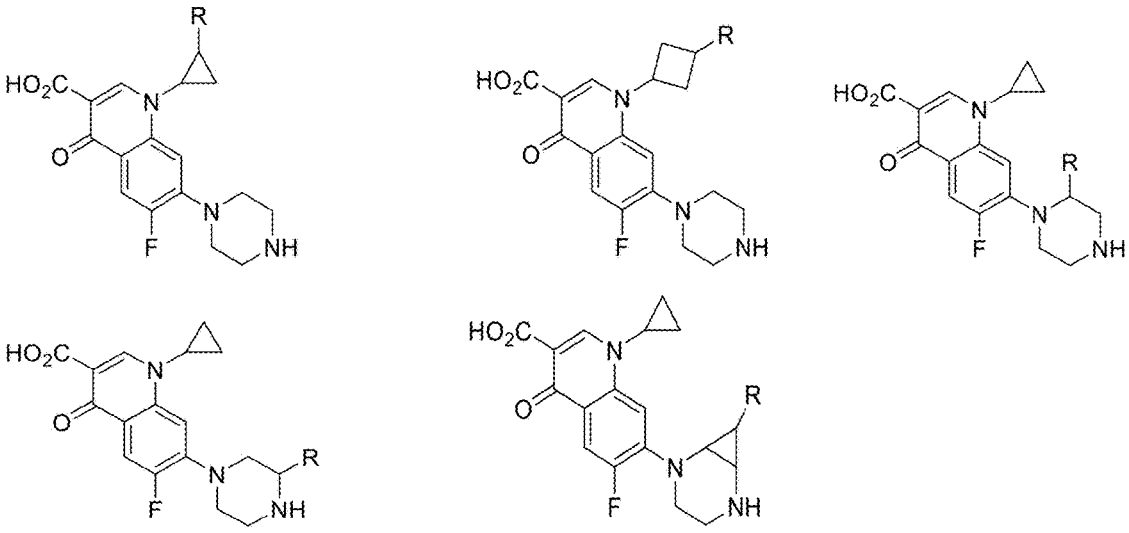


FIG. 2DDDD

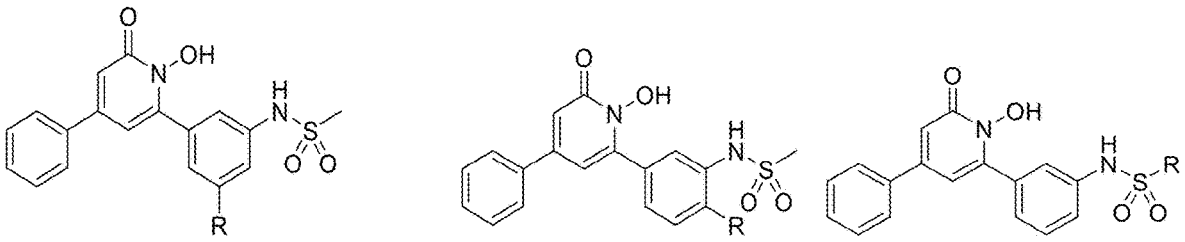


FIG. 2EEEE

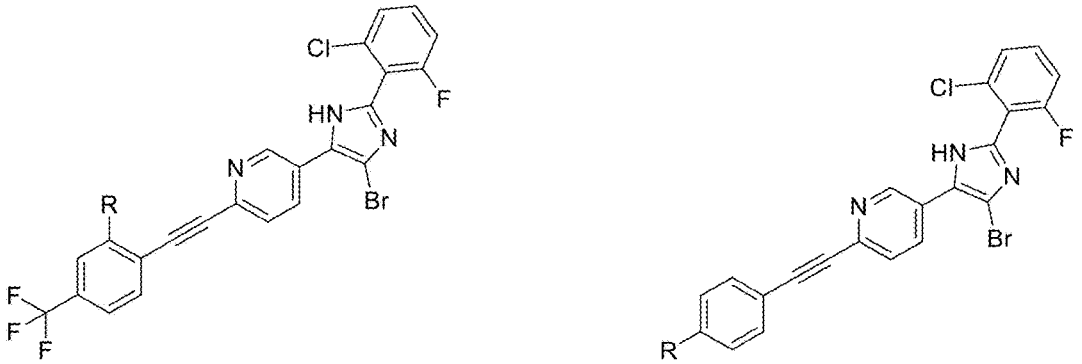


FIG. 2FFFF

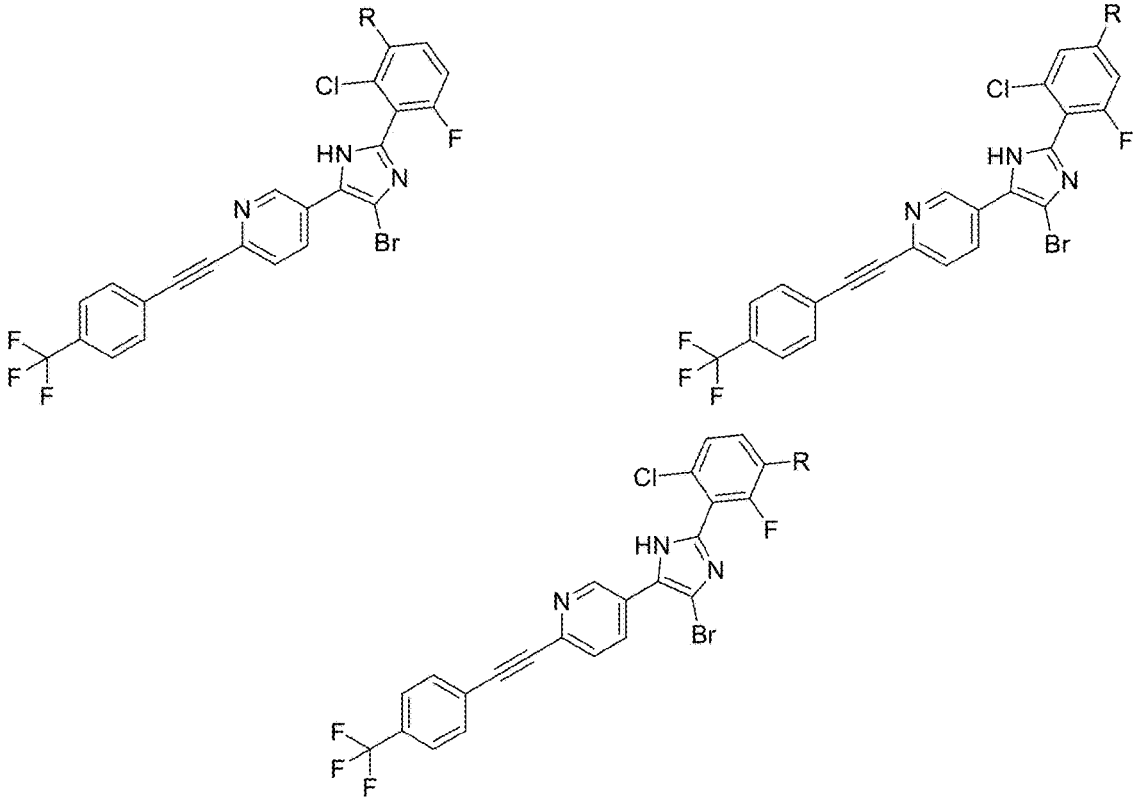


FIG. 2GGGG

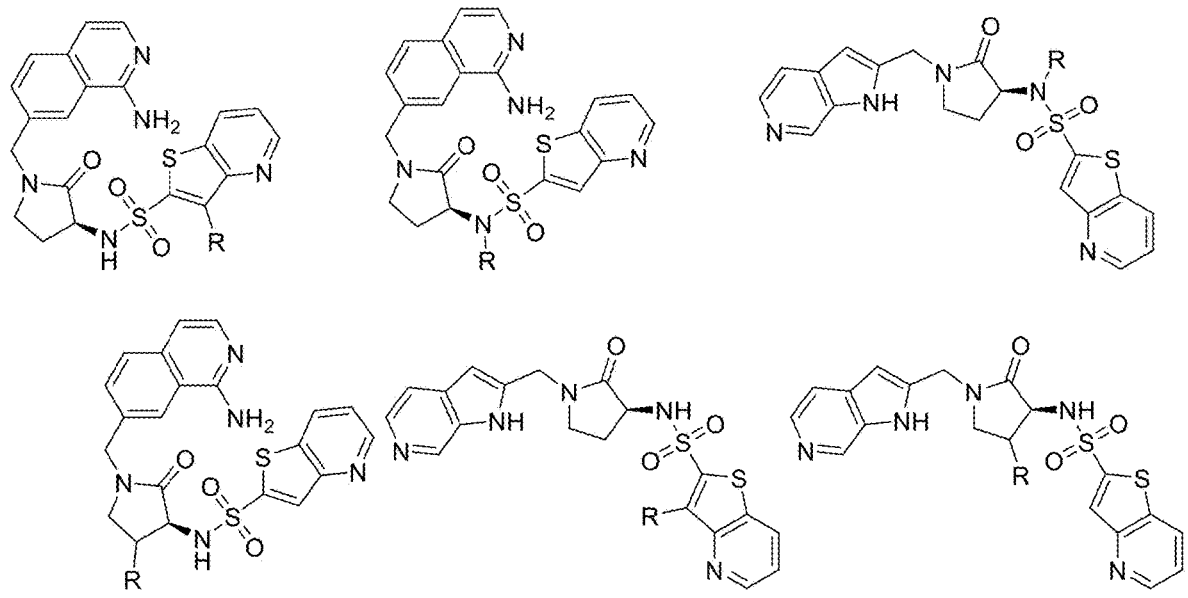


FIG. 2HHHH

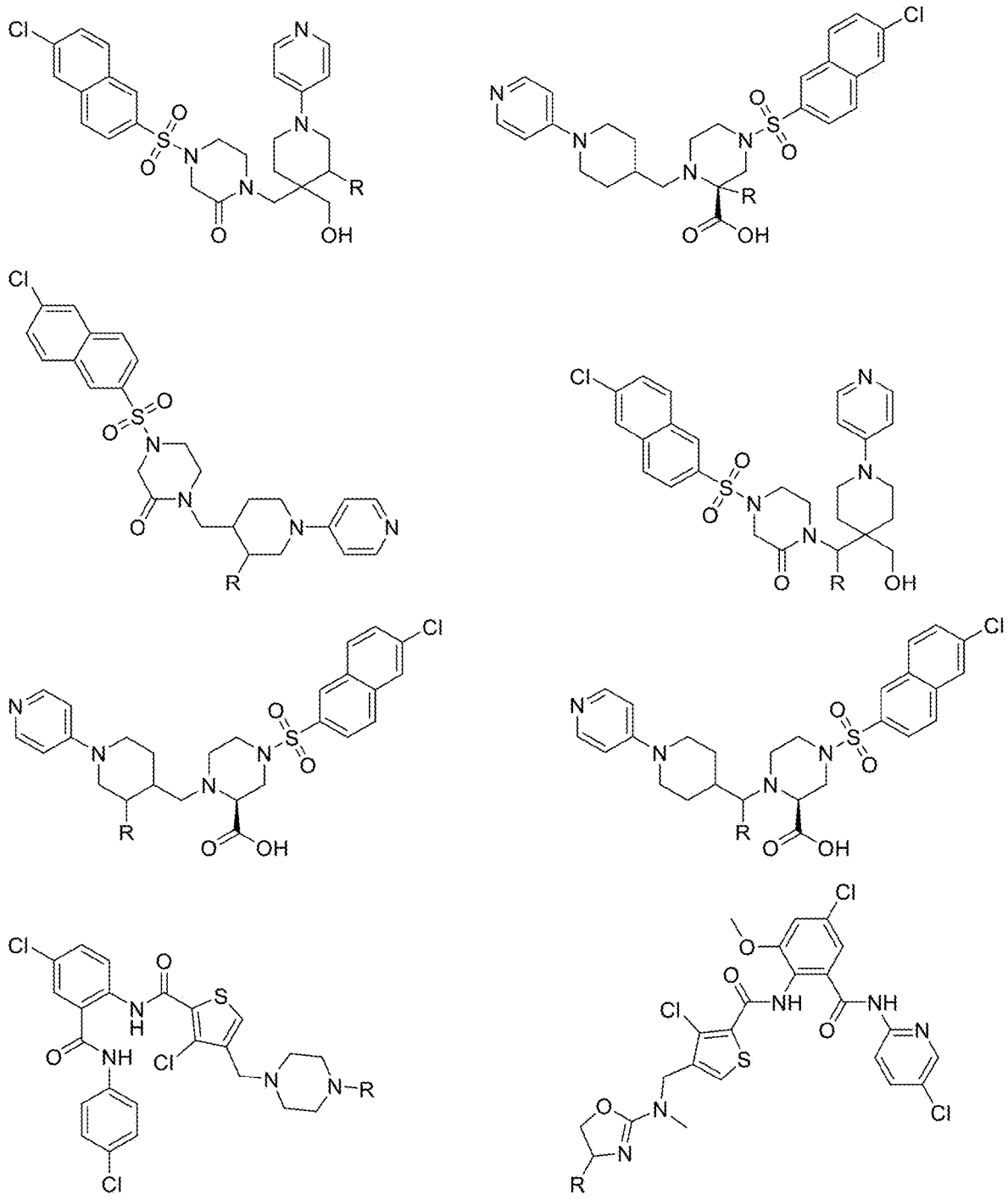


FIG. 2IIII

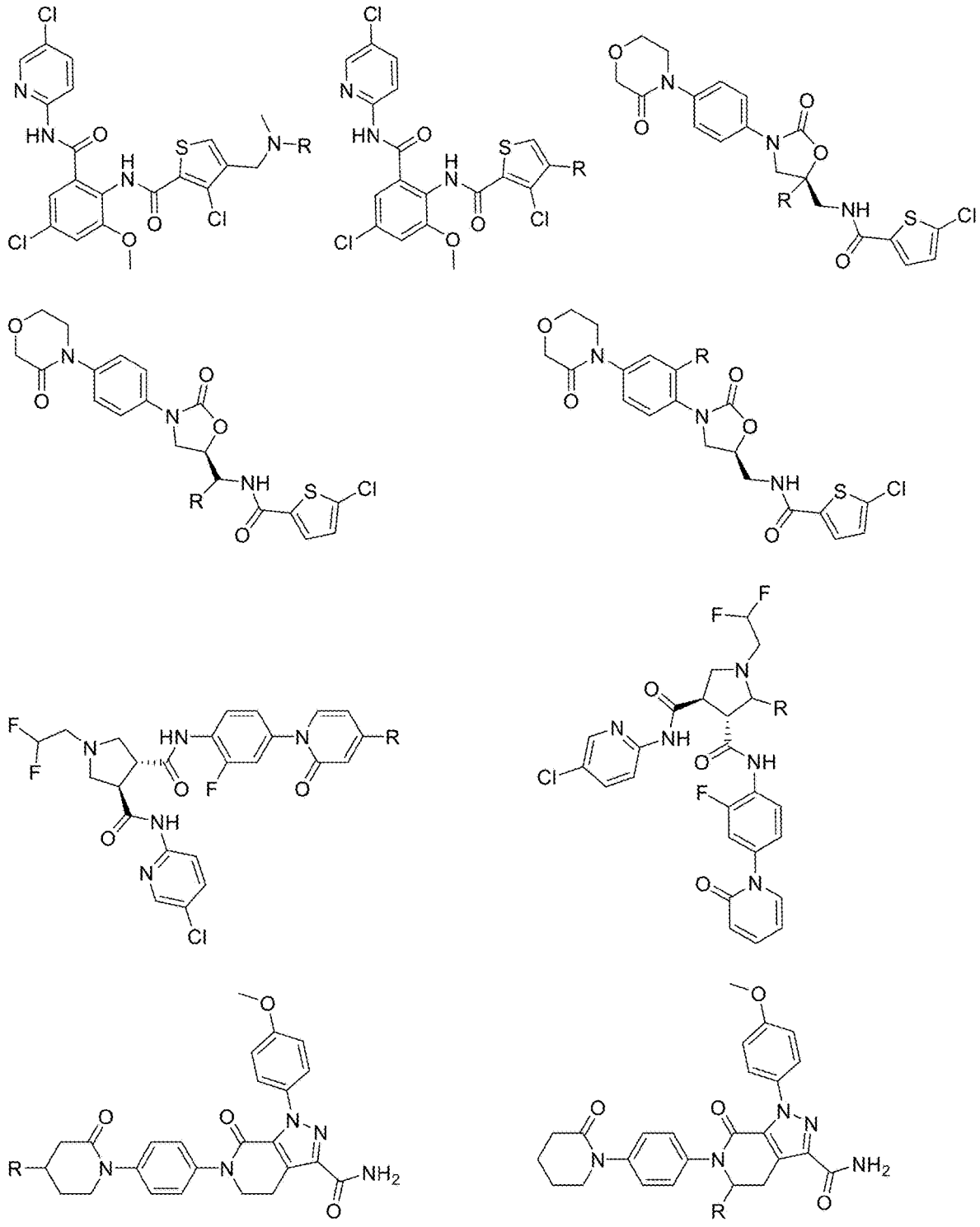


FIG. 2JJJ

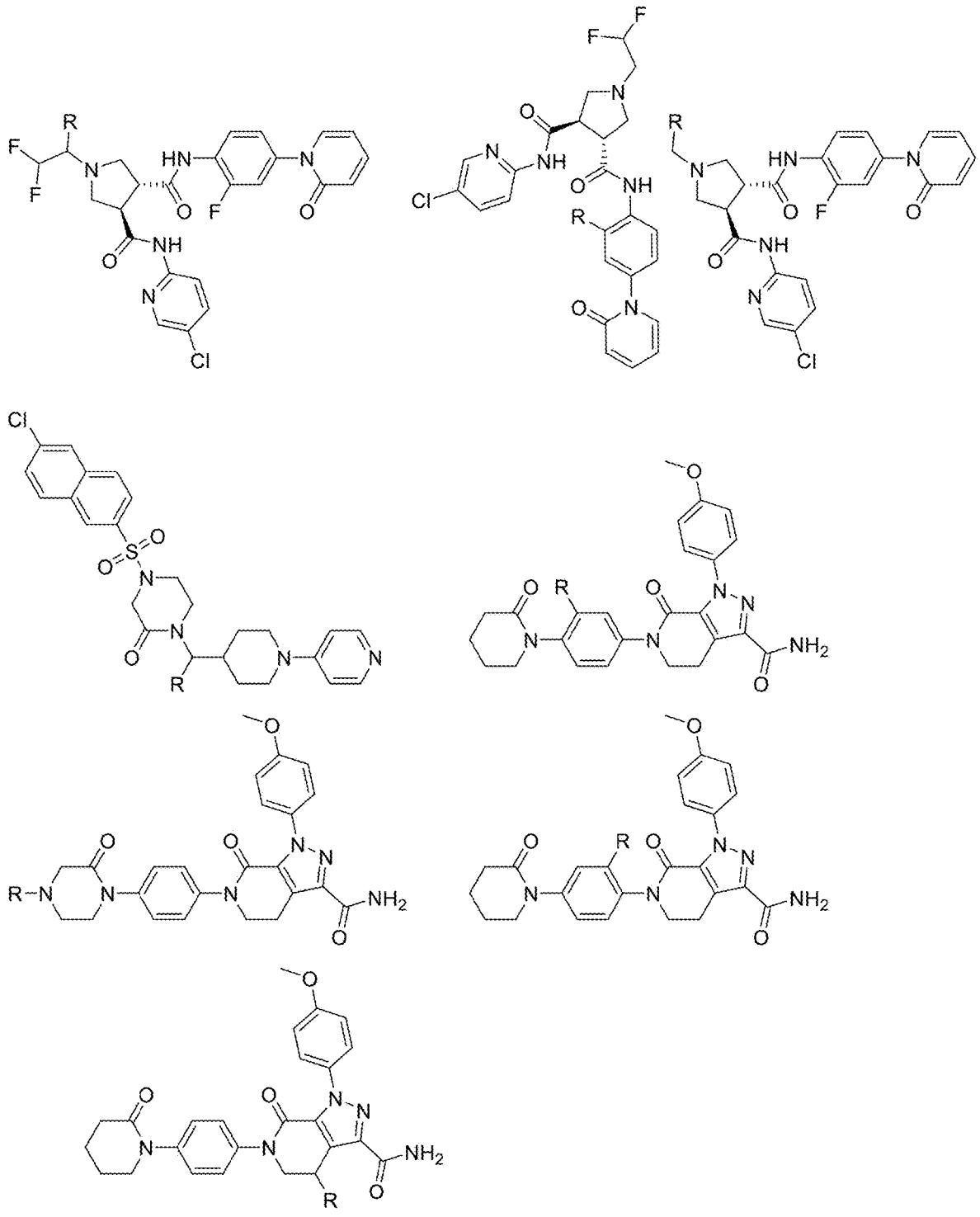


FIG. 2KKKK

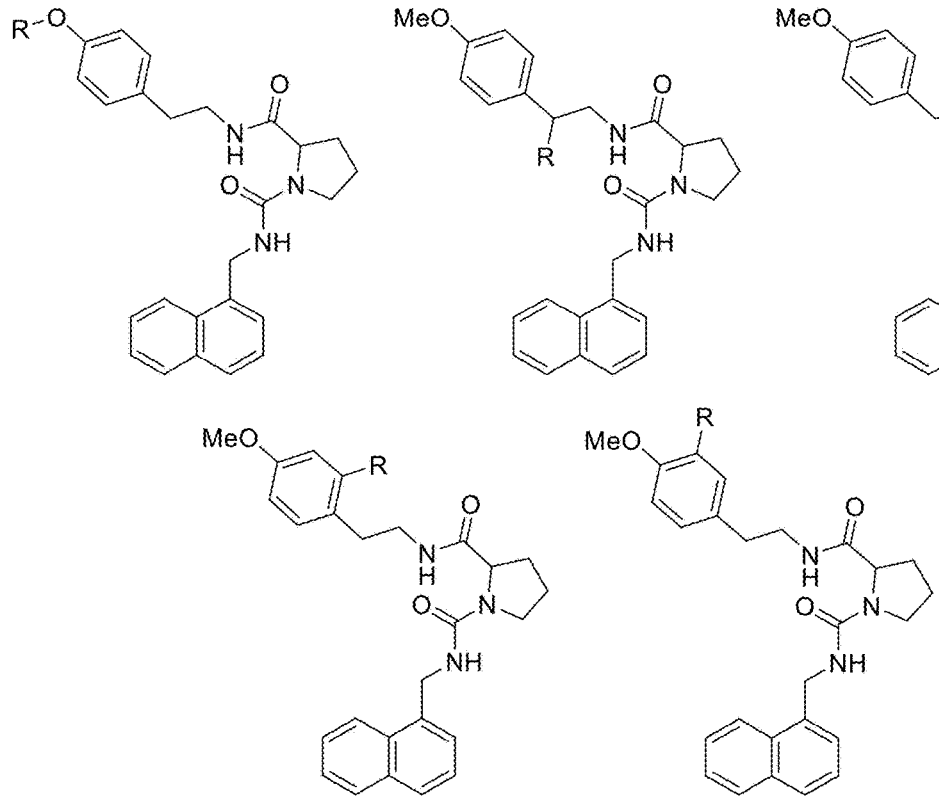


FIG. 2LLLL

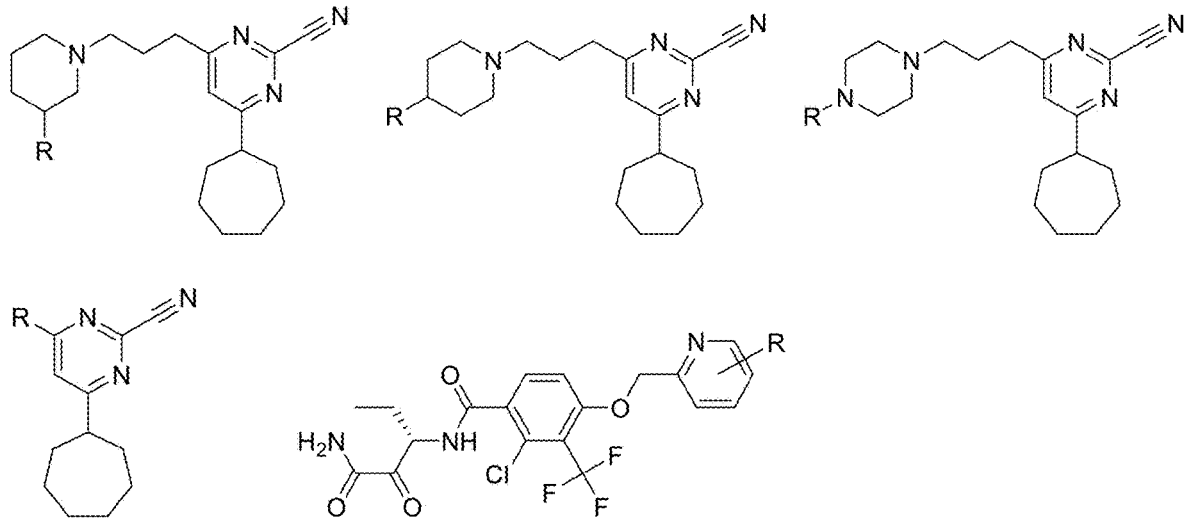


FIG. 2MMMM

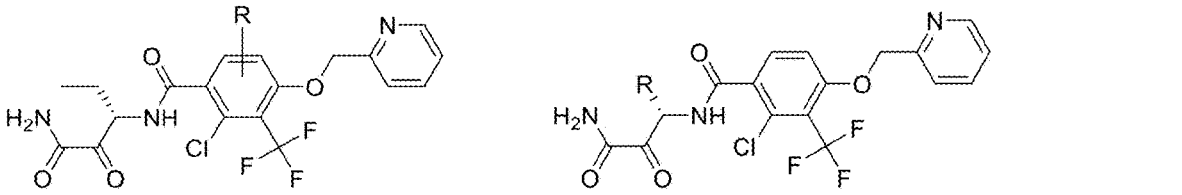


FIG. 2NNNN

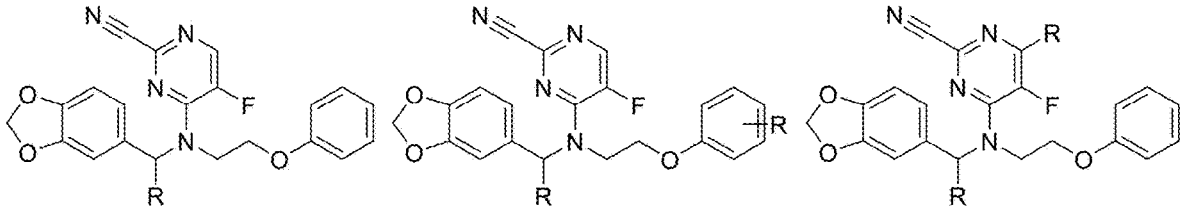


FIG. 2OOOO

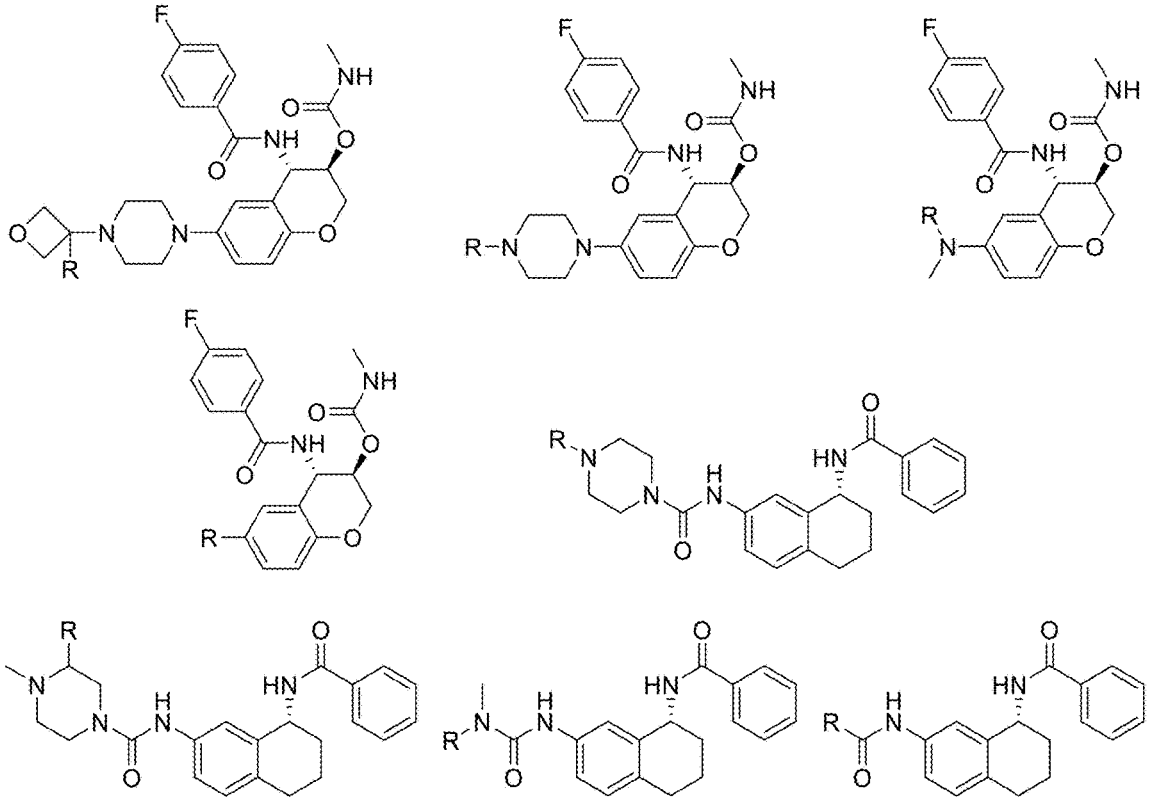


FIG. 2PPPP

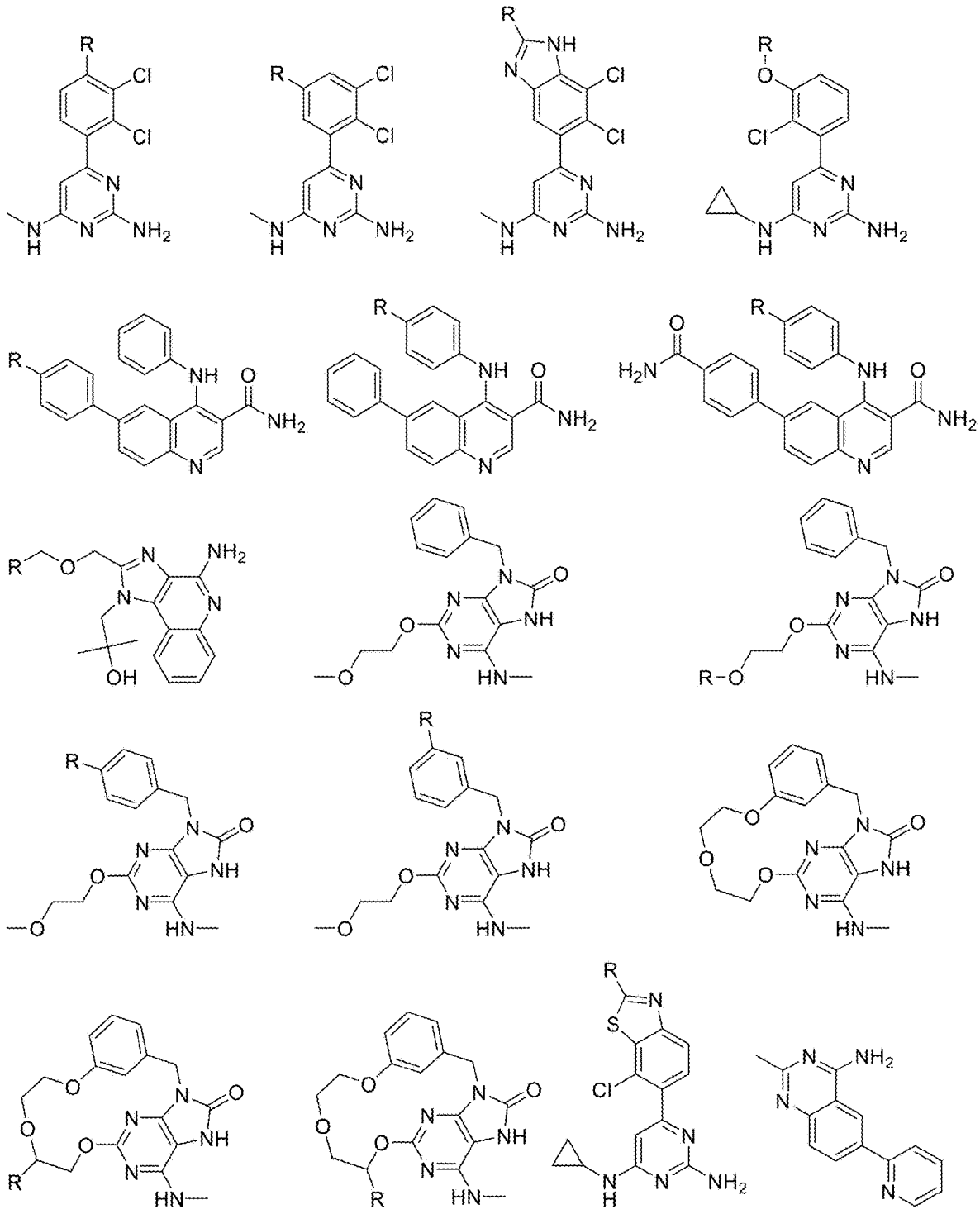


FIG. 2QQQQ

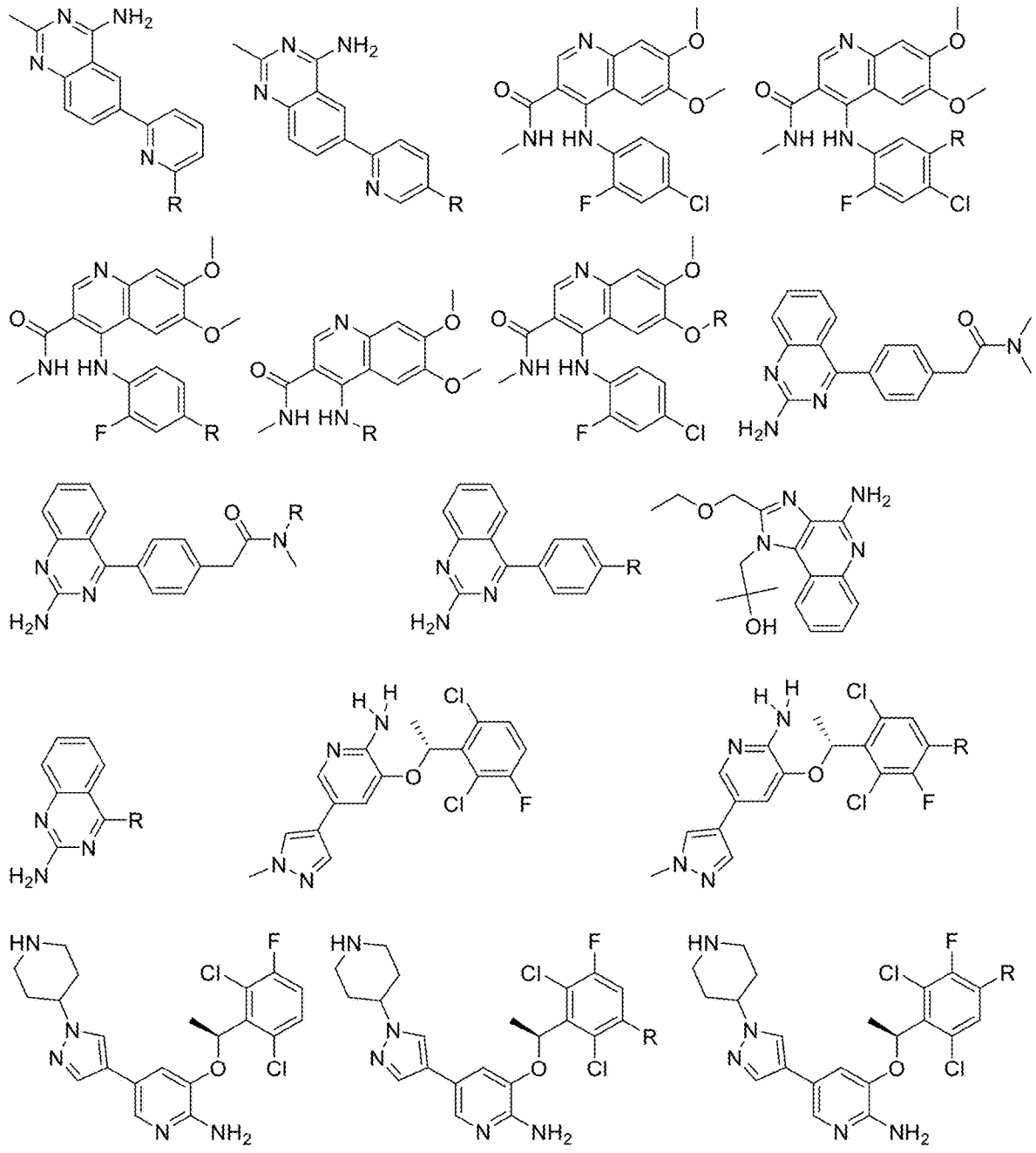


FIG. 2RRRR

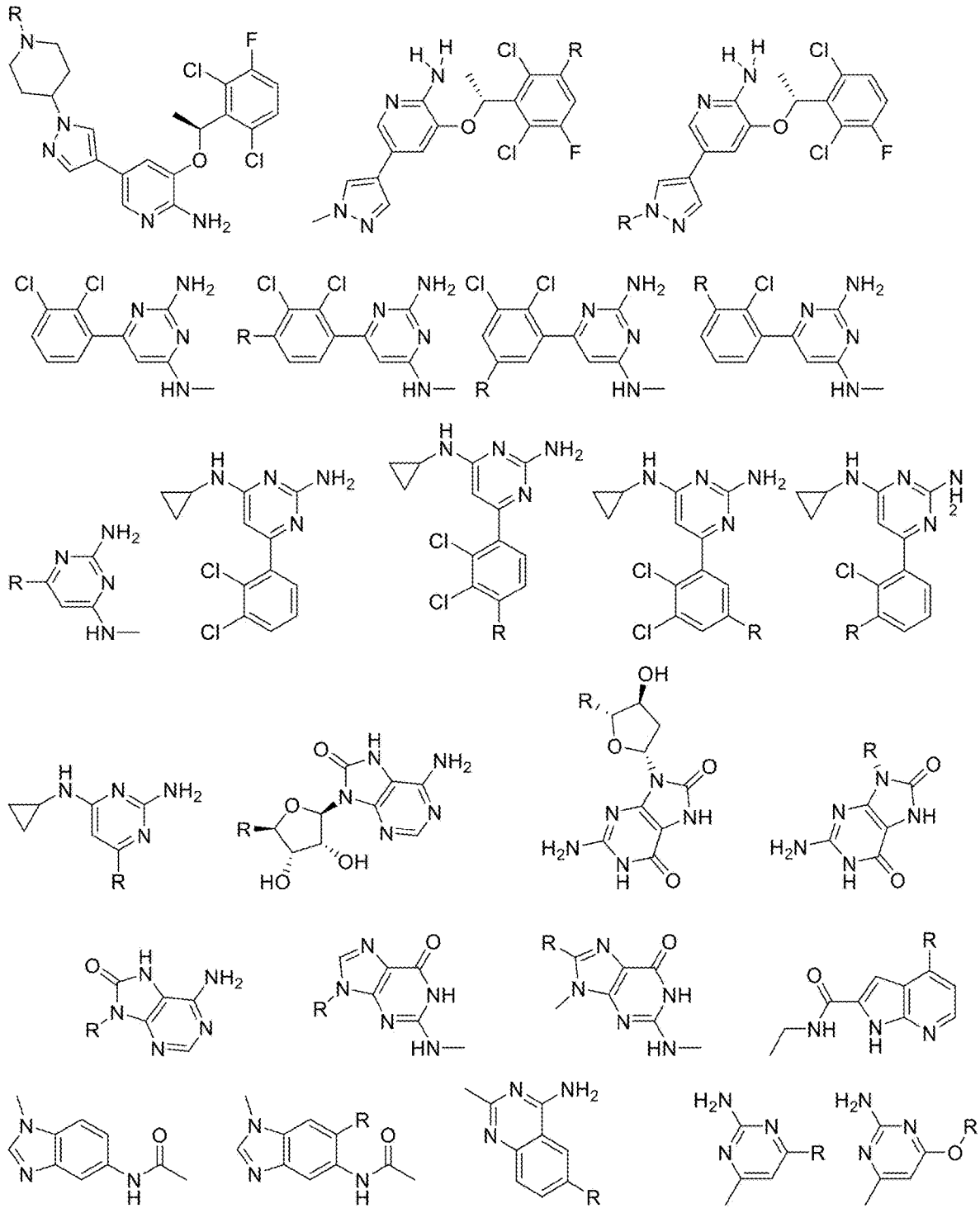


FIG. 2SSSS

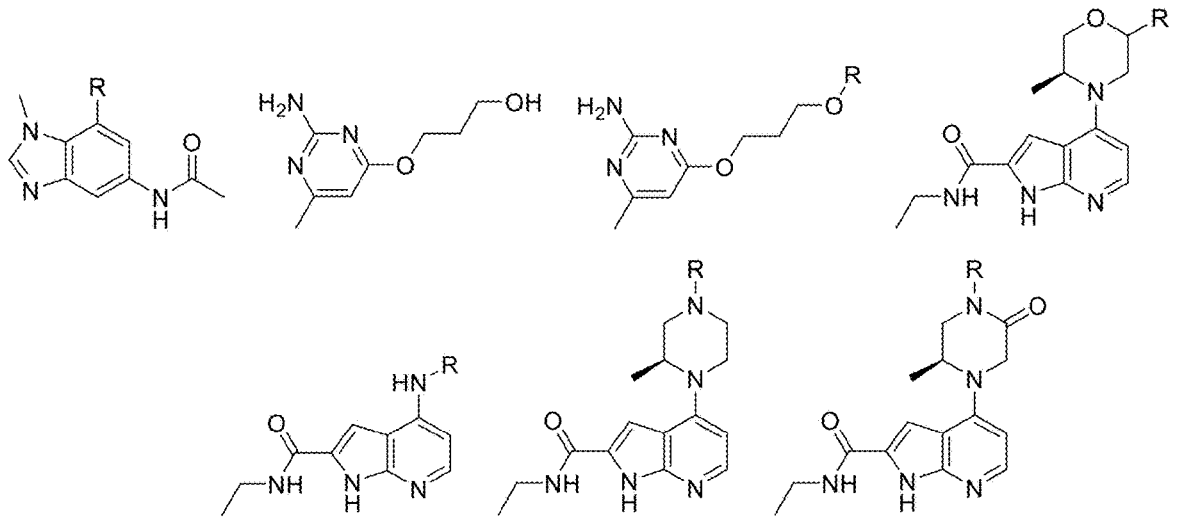


FIG. 2TTTT

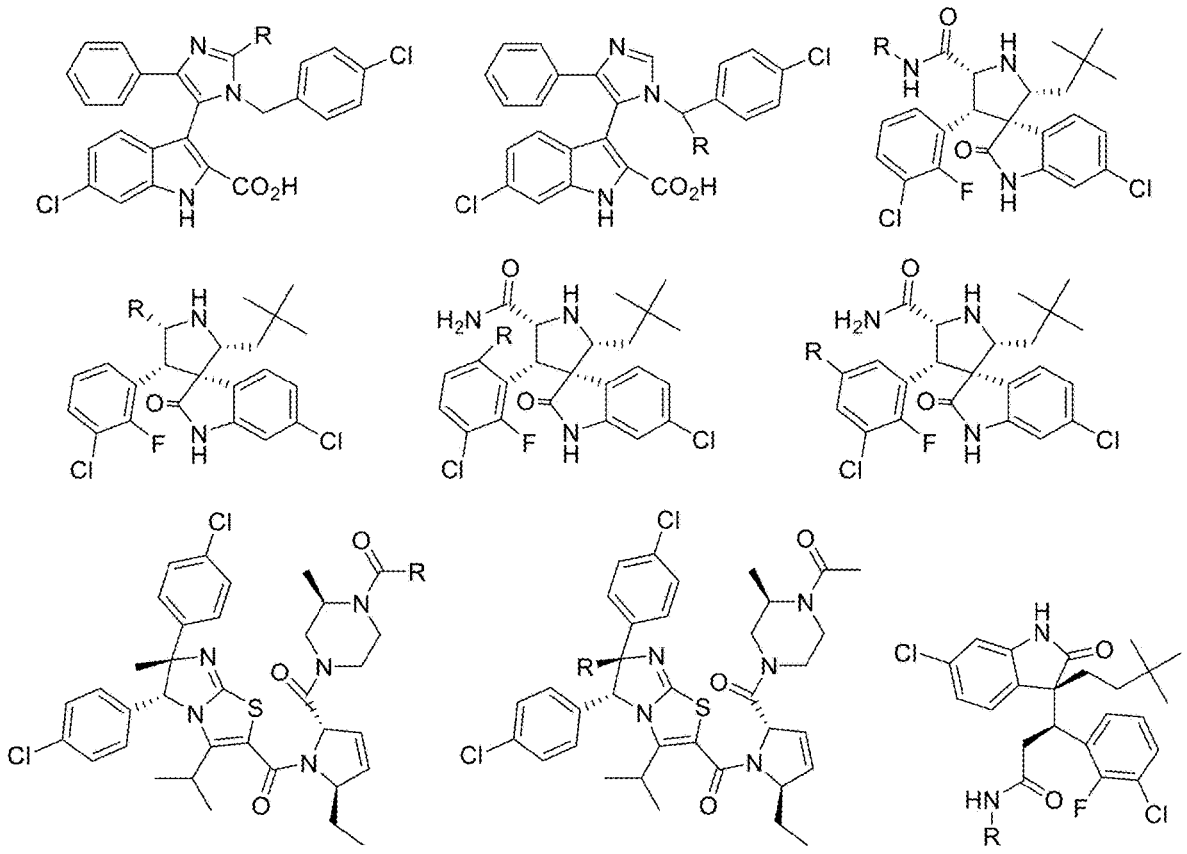


FIG. 2UUUU

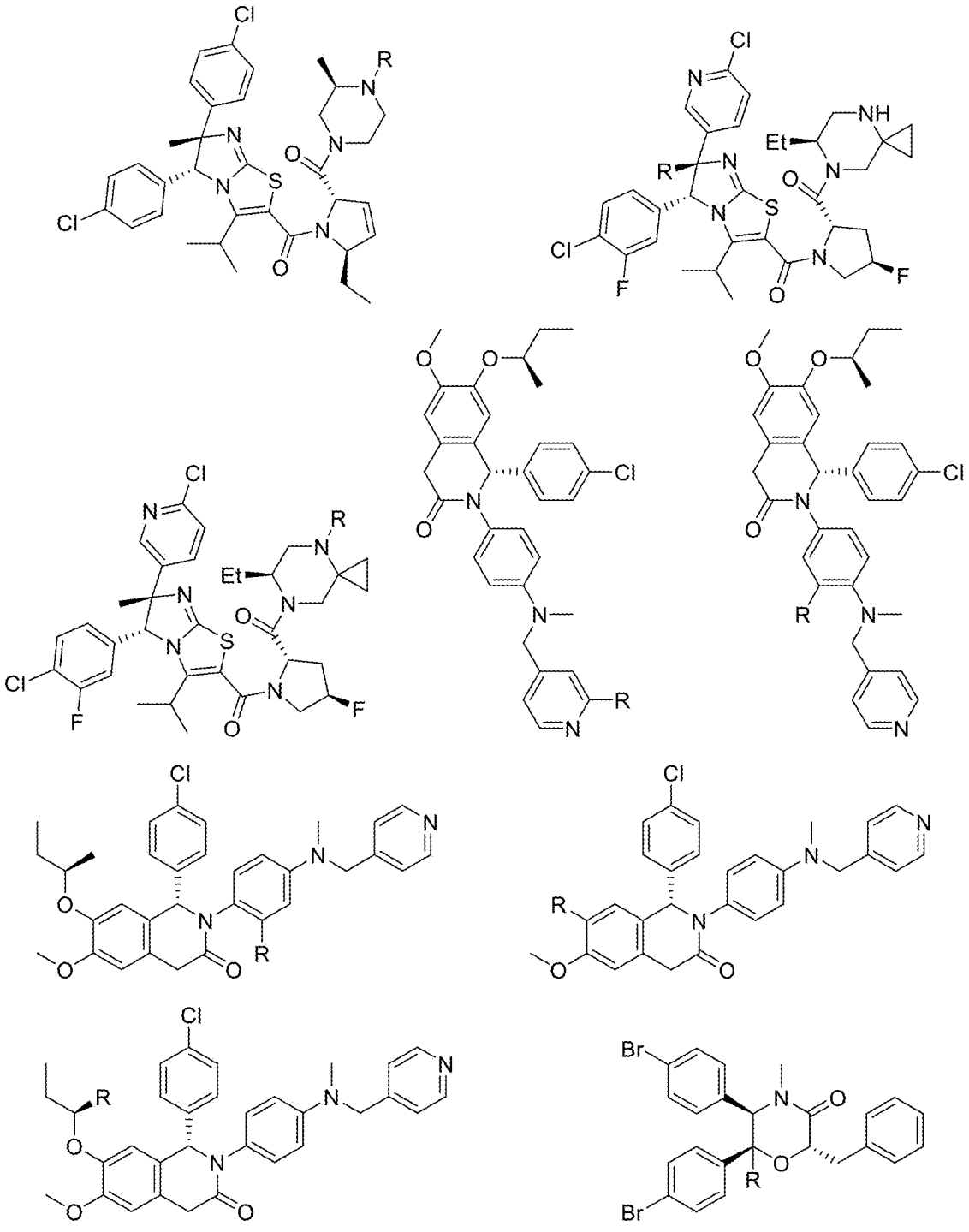


FIG. 2VVVV

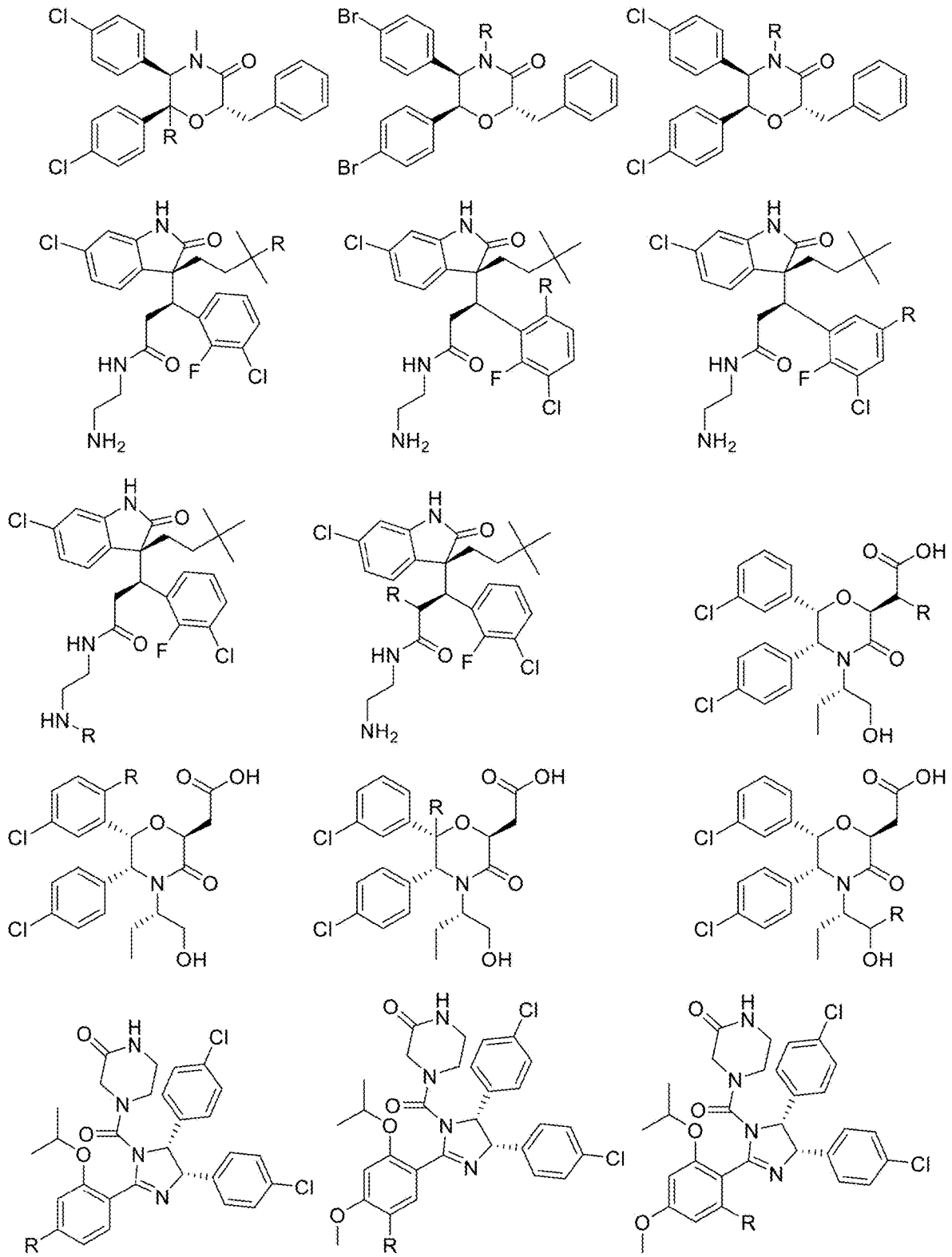


FIG. 2WWWW

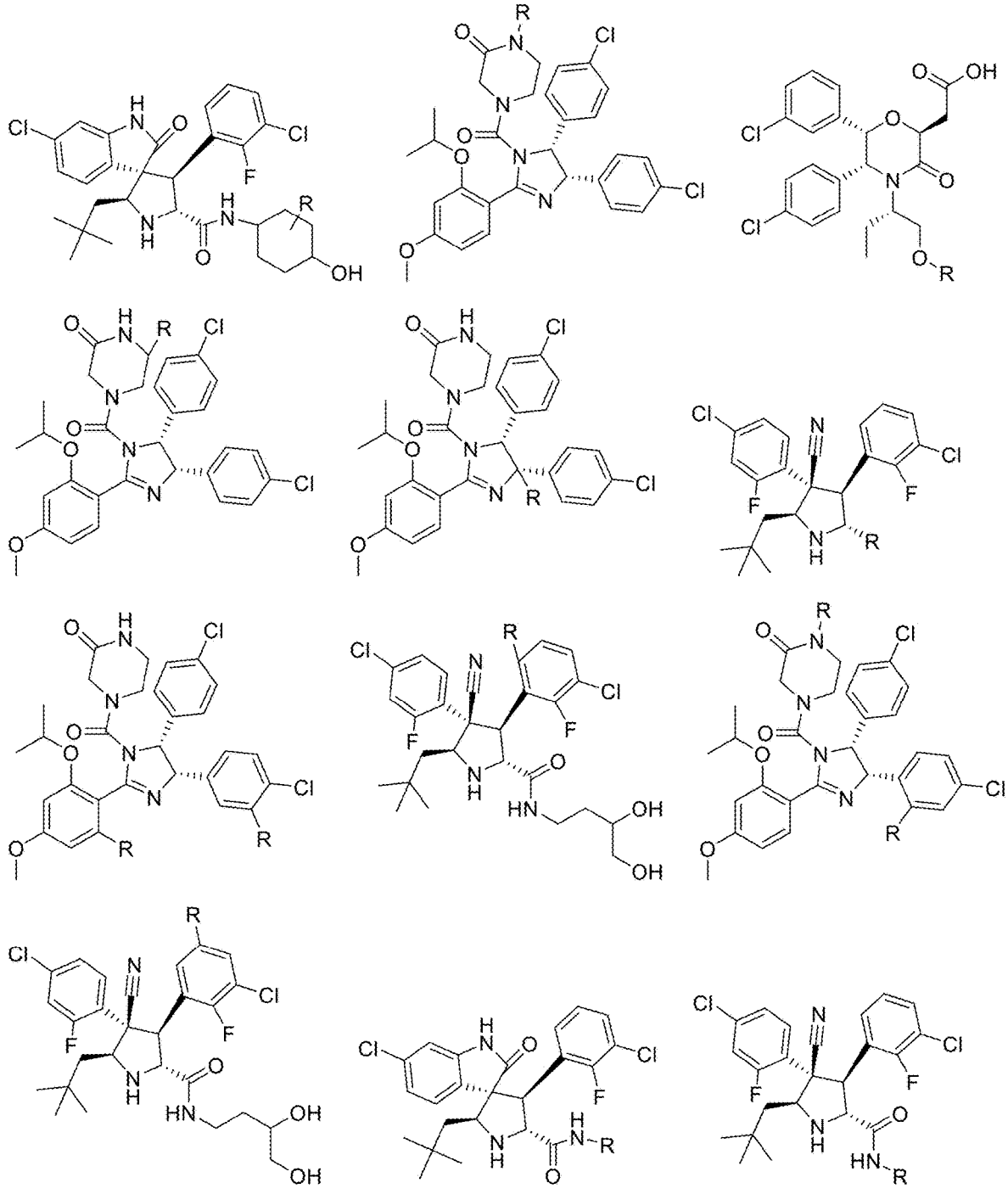


FIG. 2XXXX

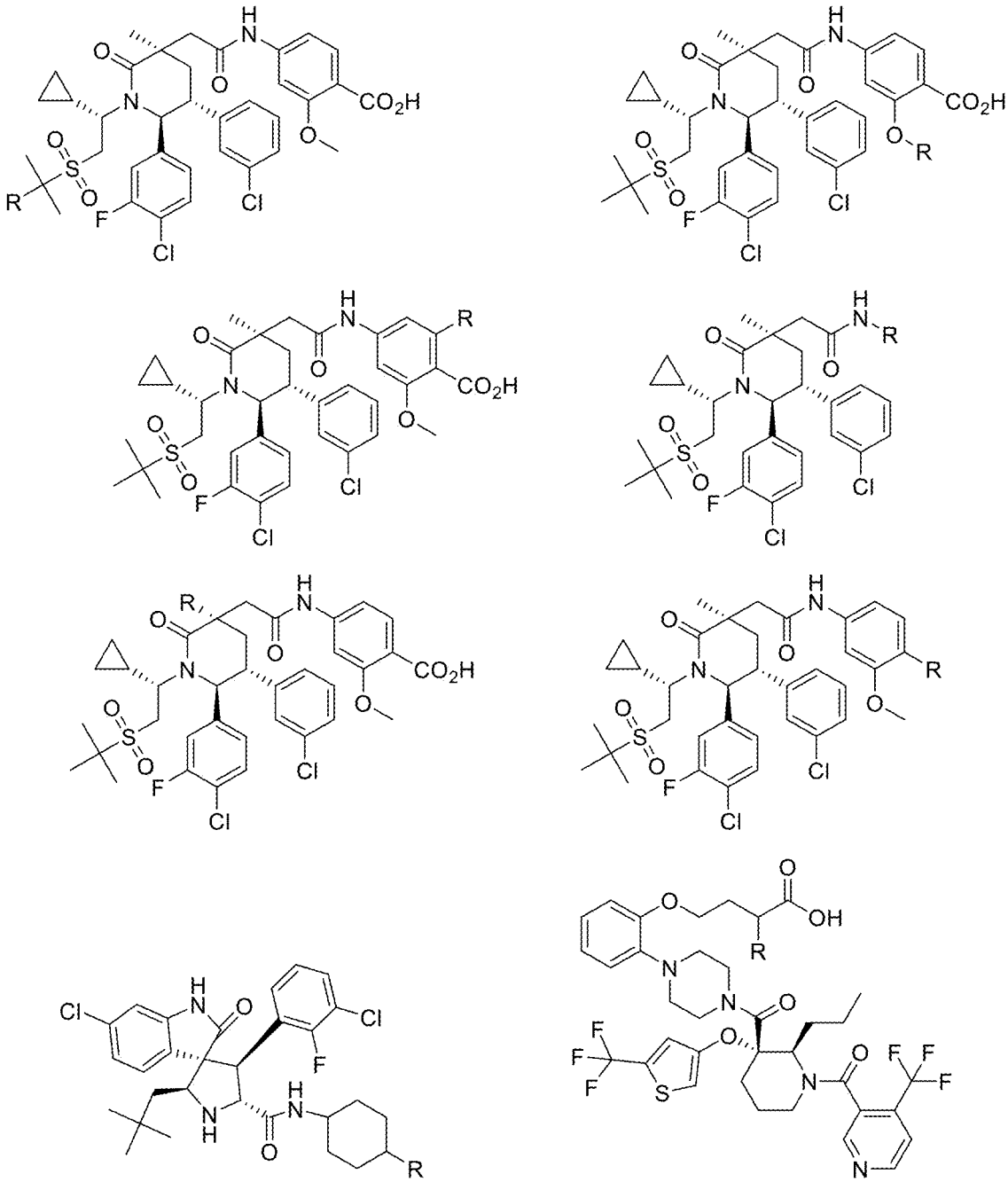


FIG. 2YYYY

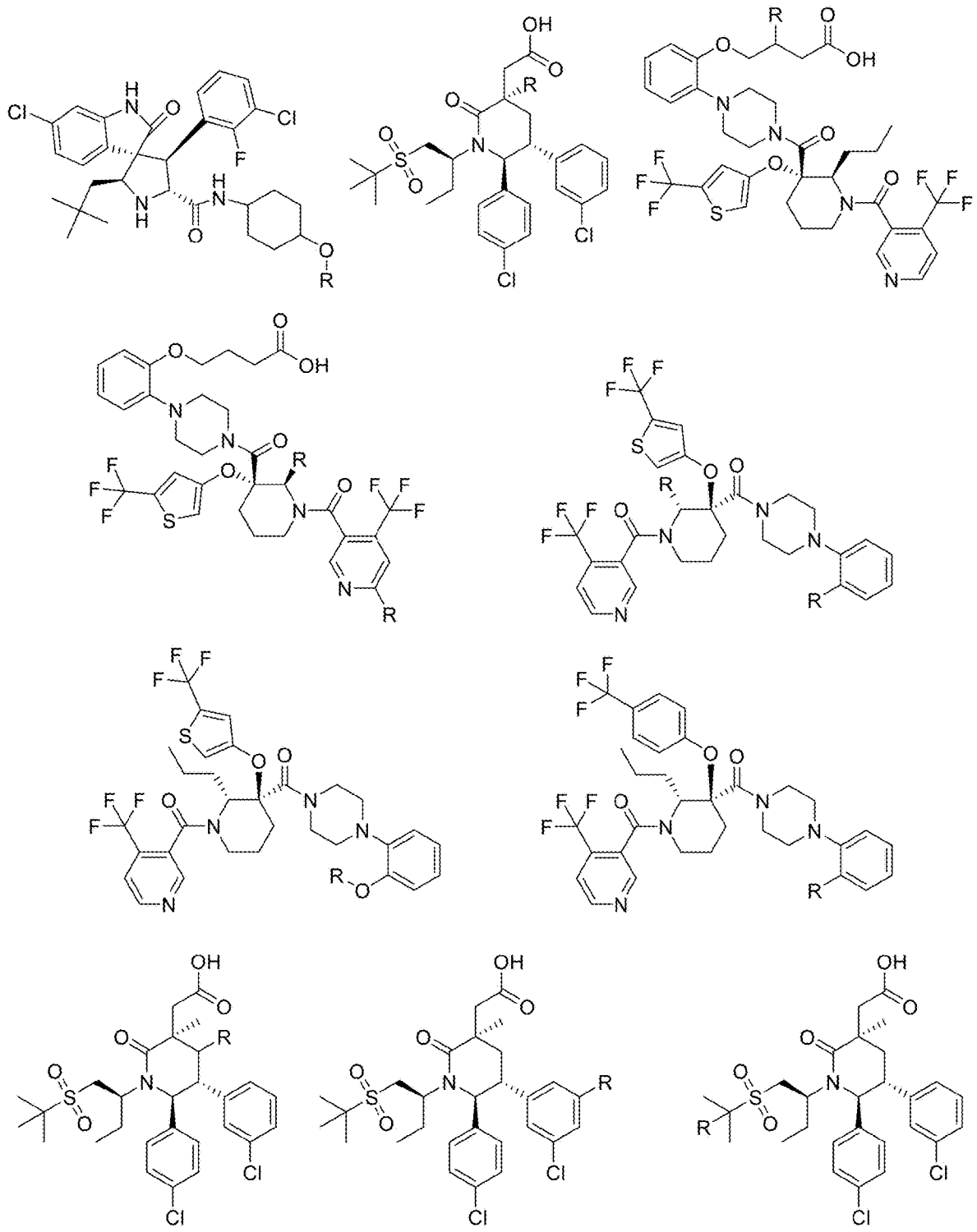


FIG. 2ZZZZ

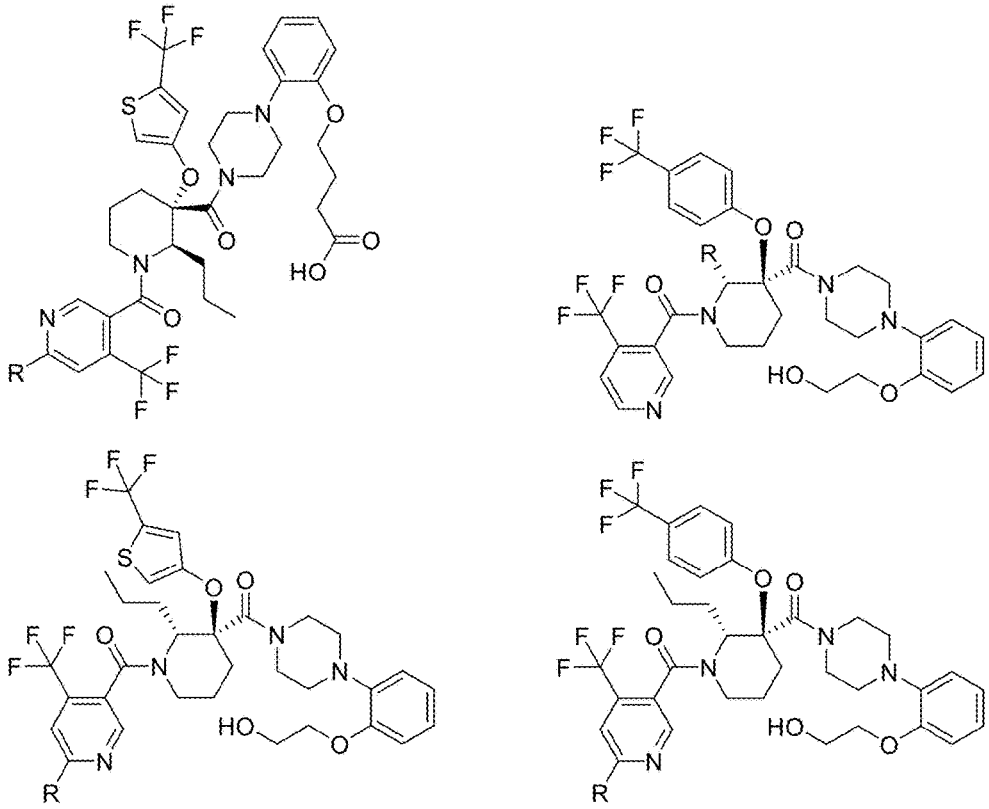


FIG. 2AAAAA

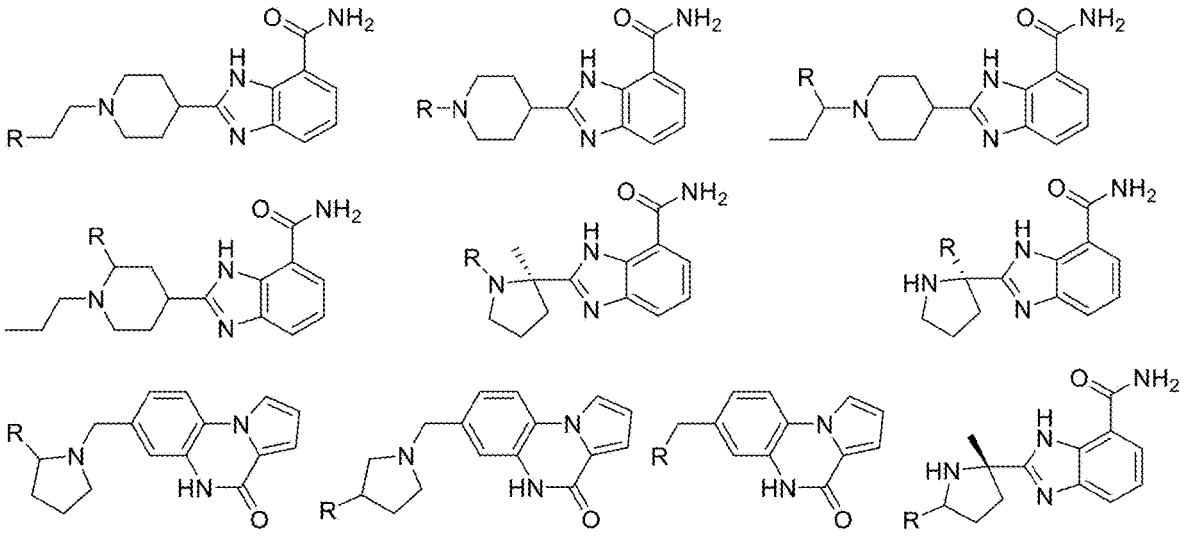


FIG. 2BBBBB

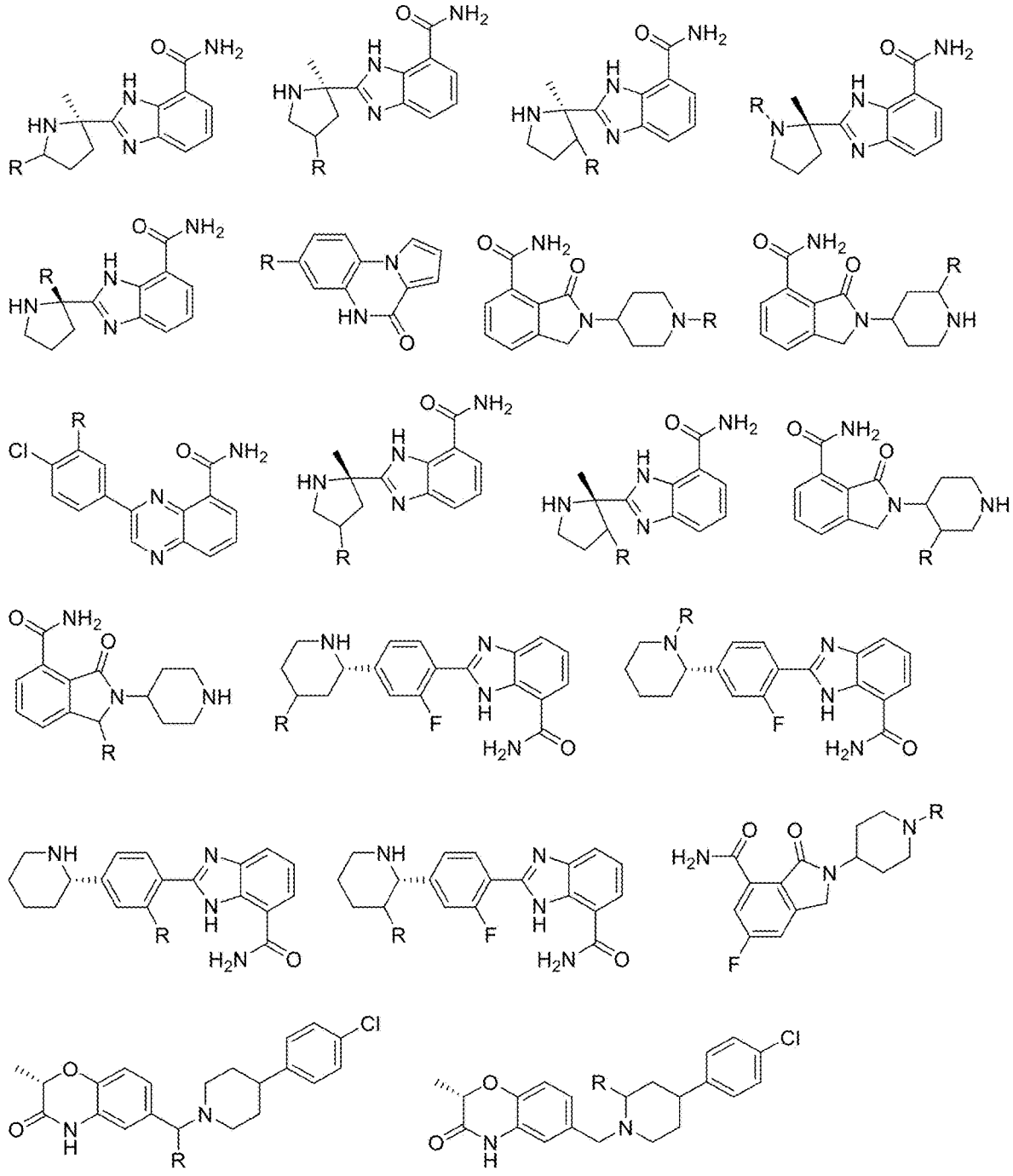
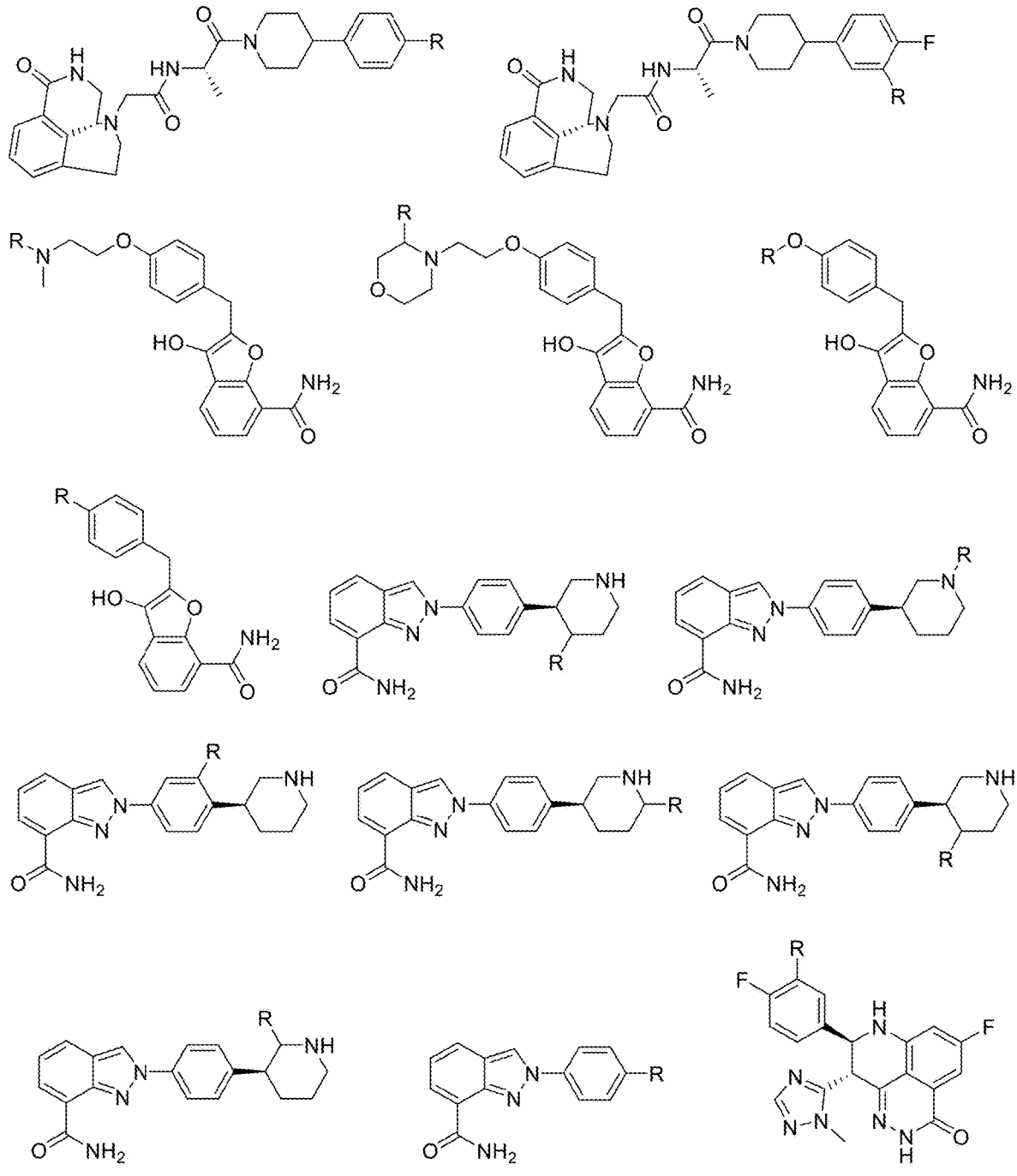


FIG. 2CCCCC



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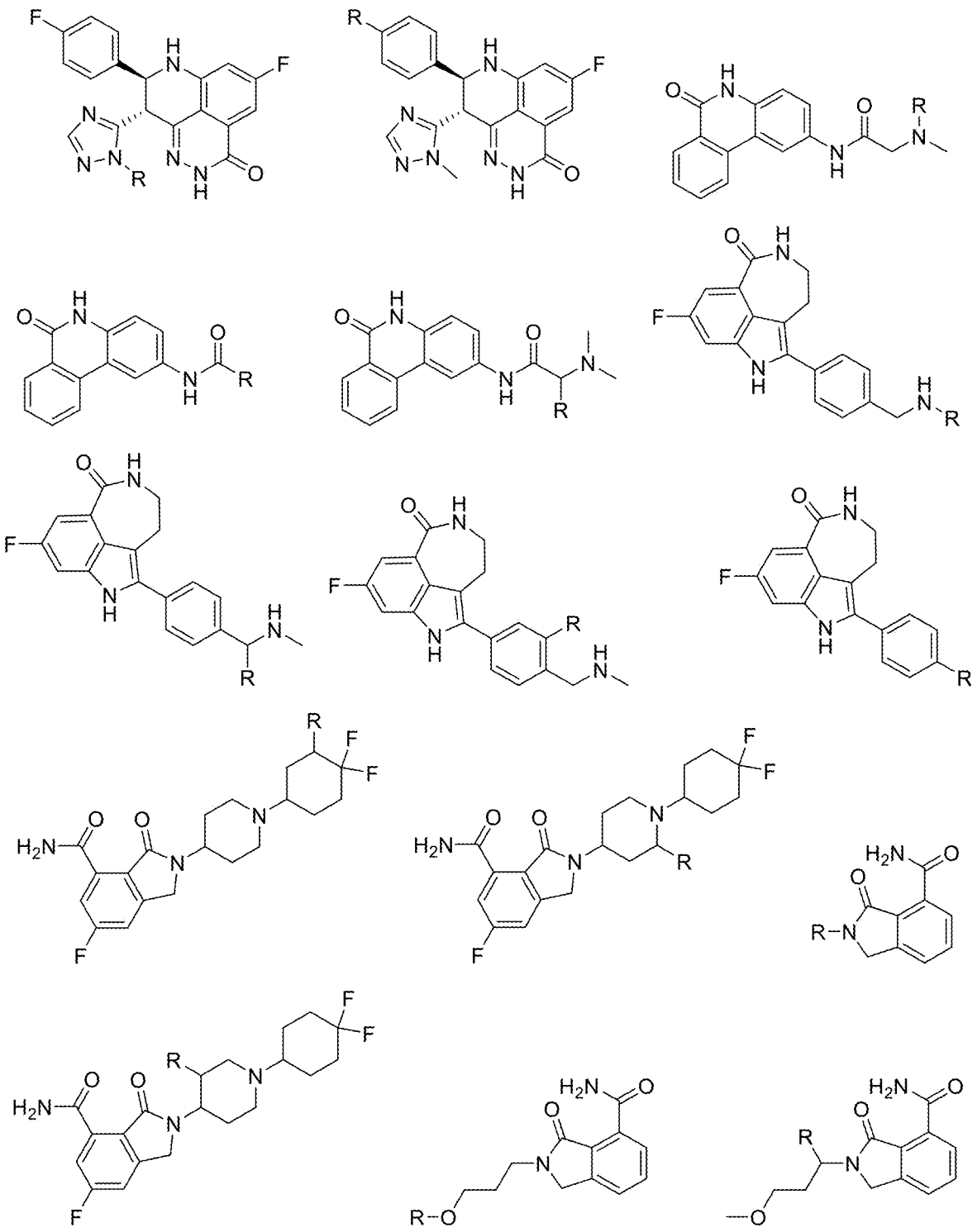


FIG. 2EEEEE

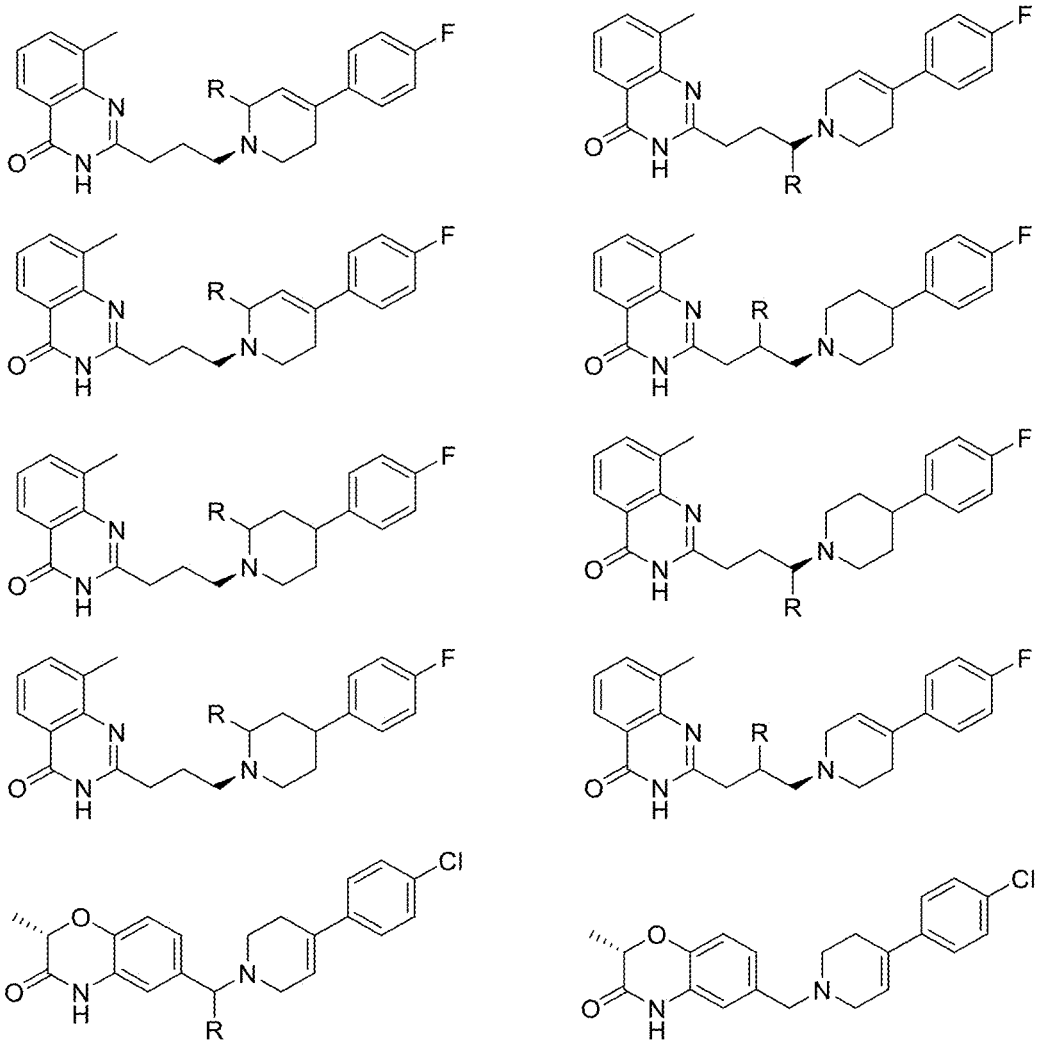


FIG. 2FFFFF

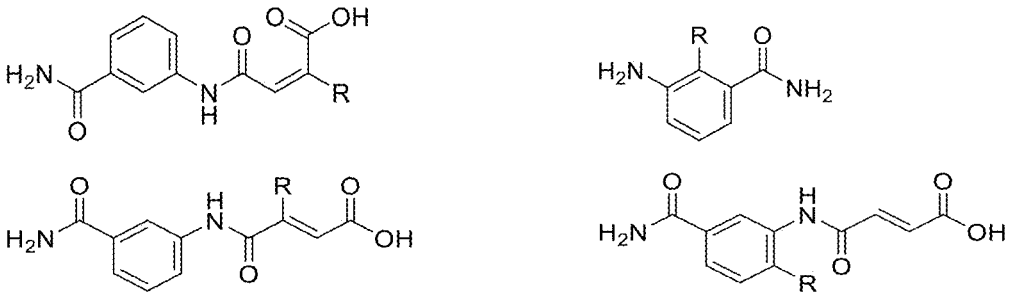


FIG. 2GGGGG

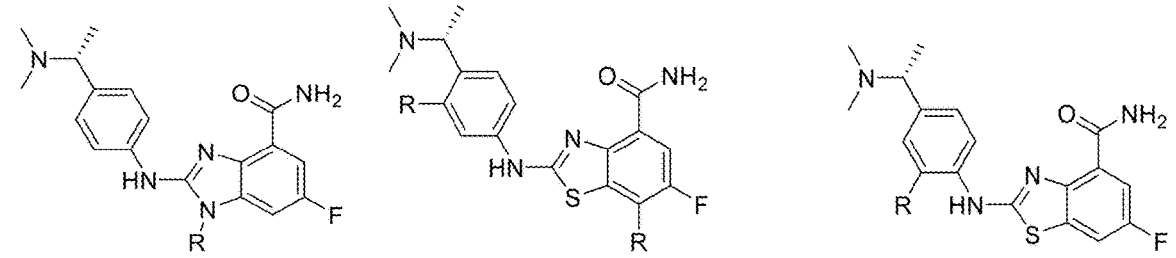


FIG. 2HHHHH

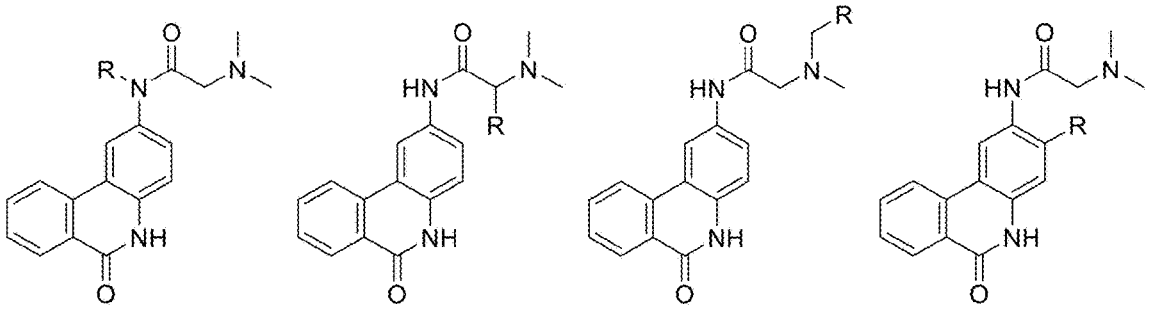


FIG. 2IIIII

FIG. 2JJJJJ

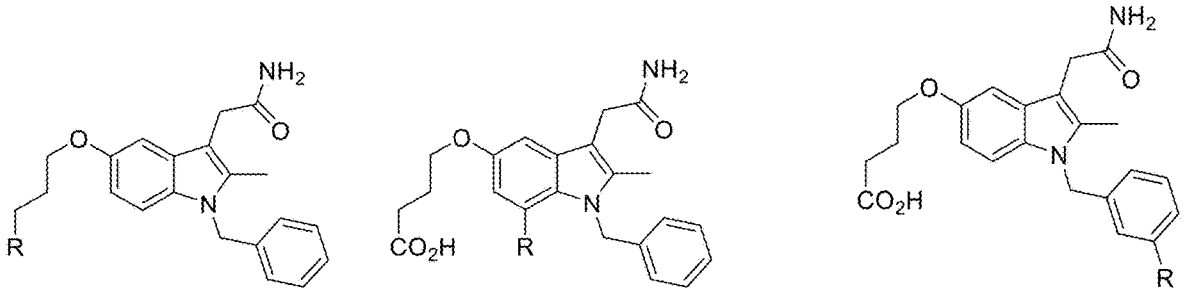


FIG. 2KKKKK

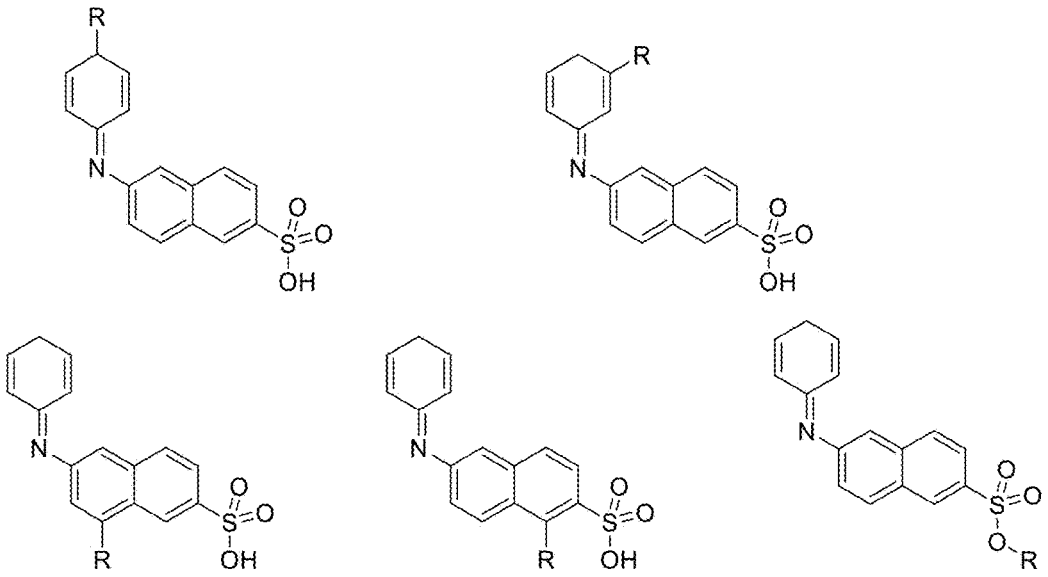


FIG. 2LLLLL

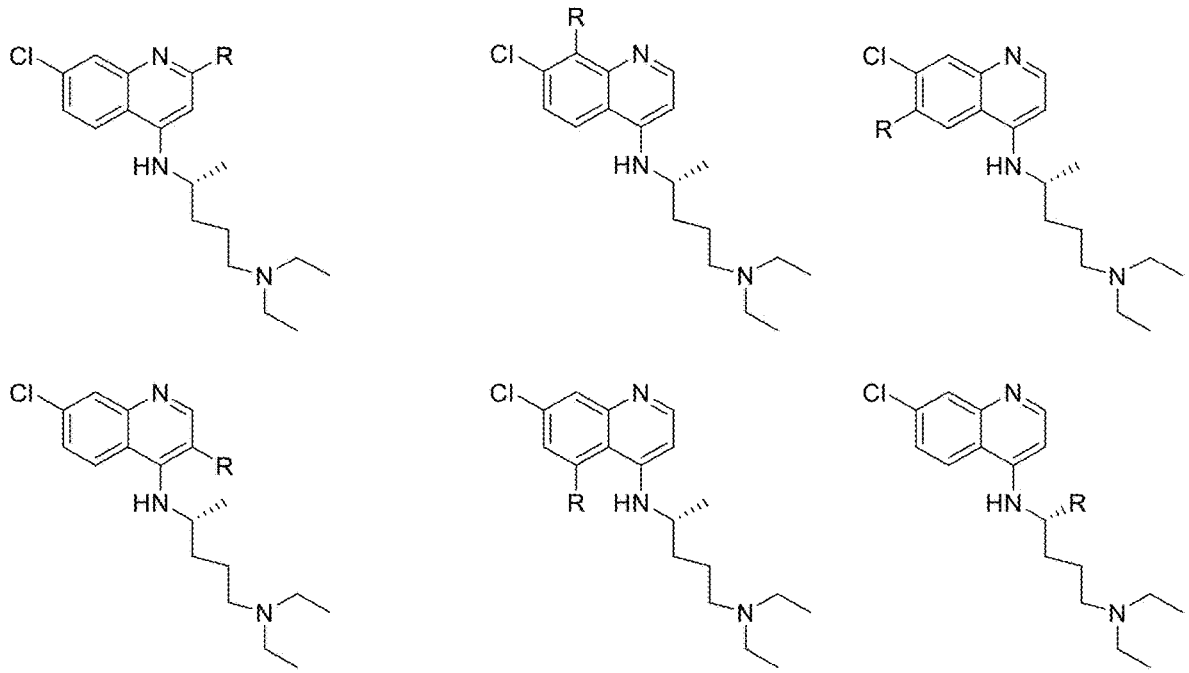


FIG. 2MMMMM

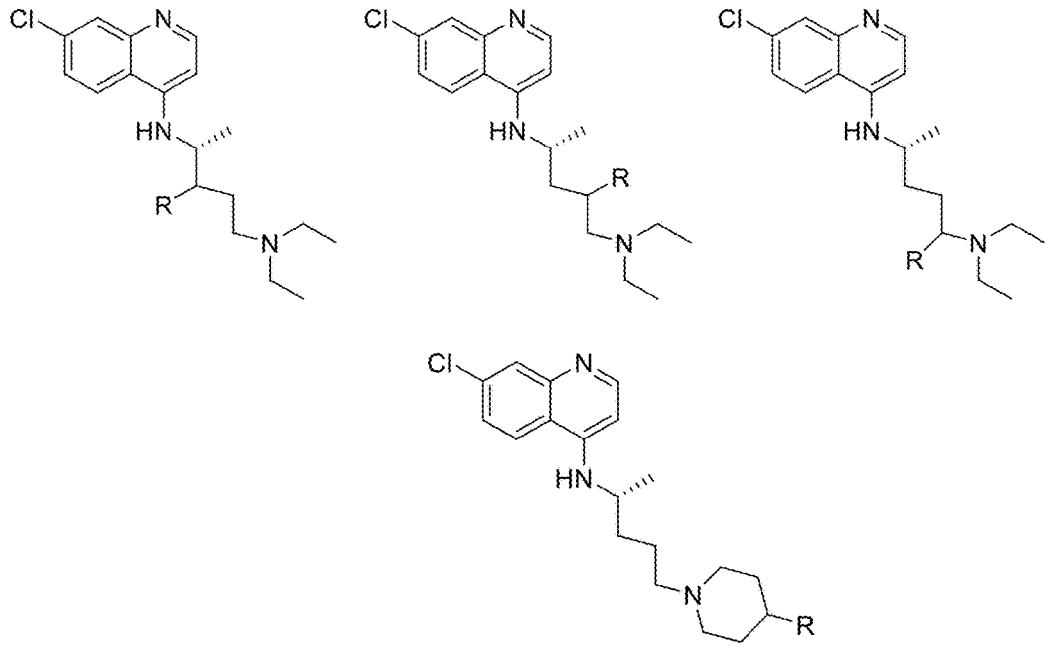


FIG. 2NNNNN

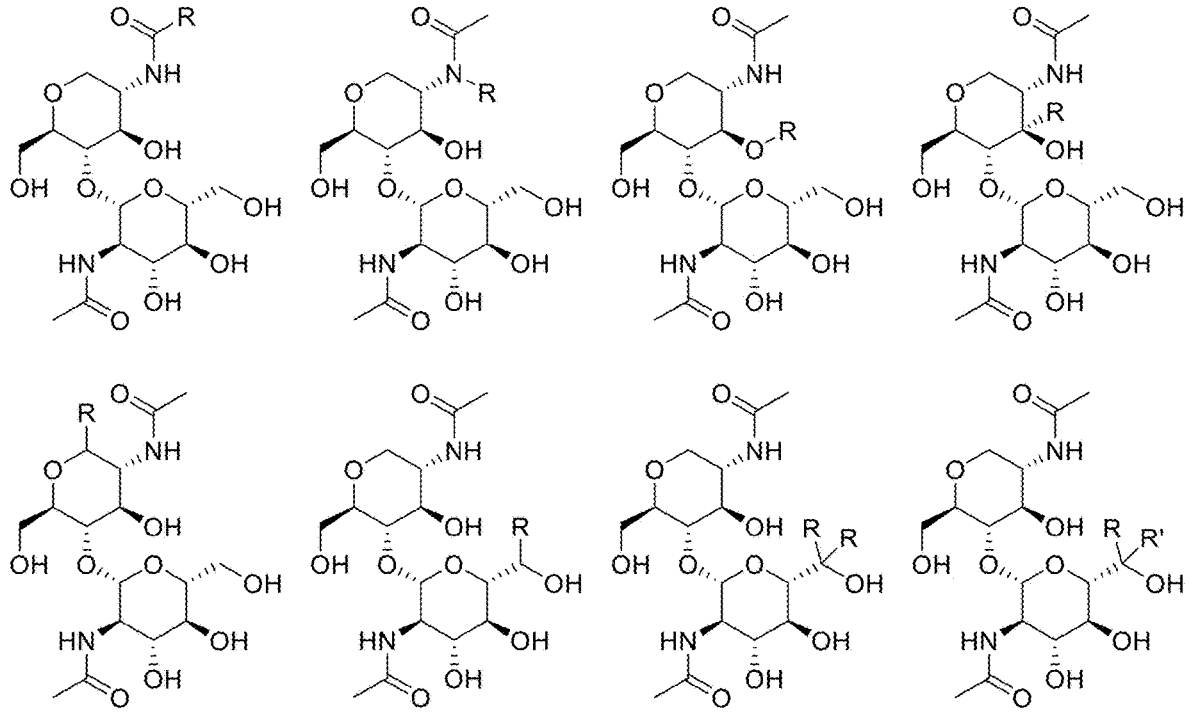


FIG. 2OOOOO

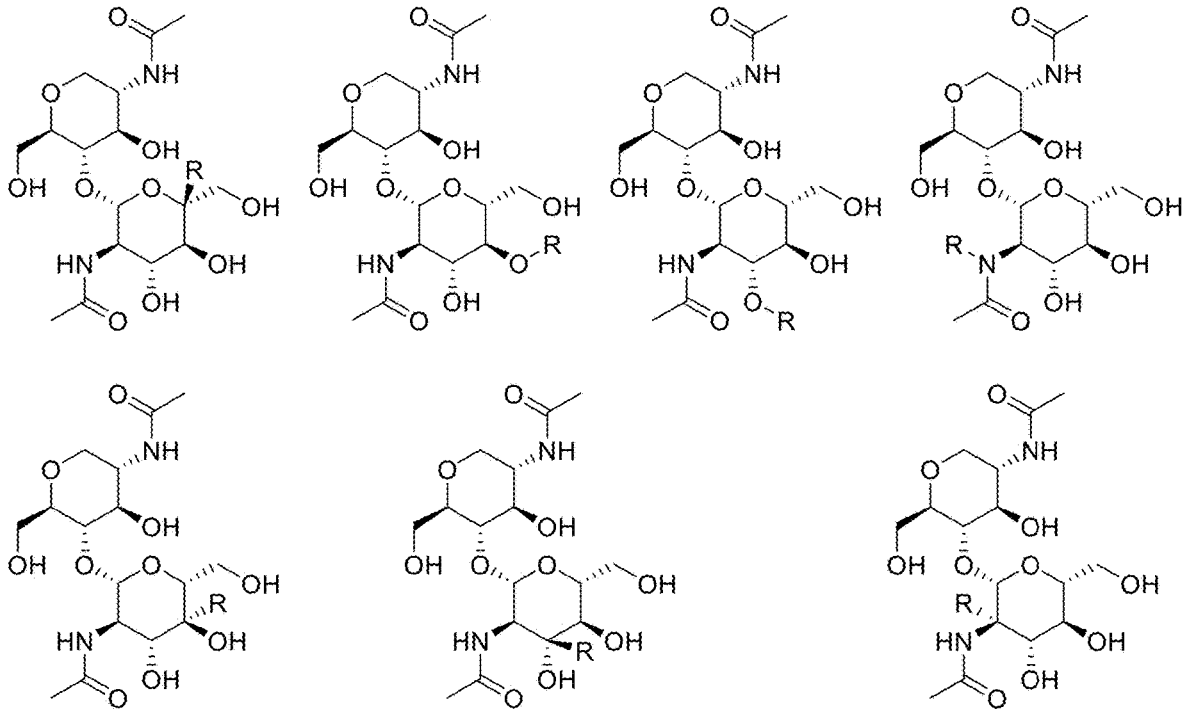


FIG. 2PPPPP

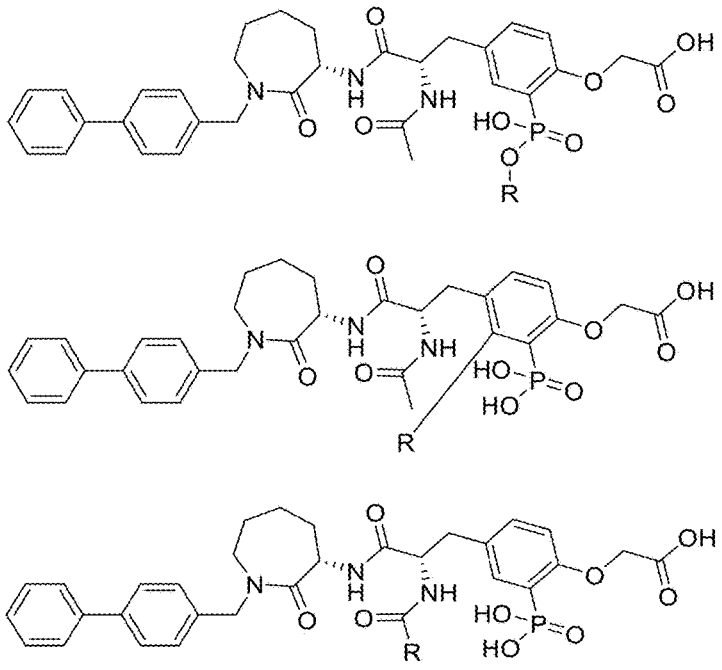


FIG. 2QQQQQ

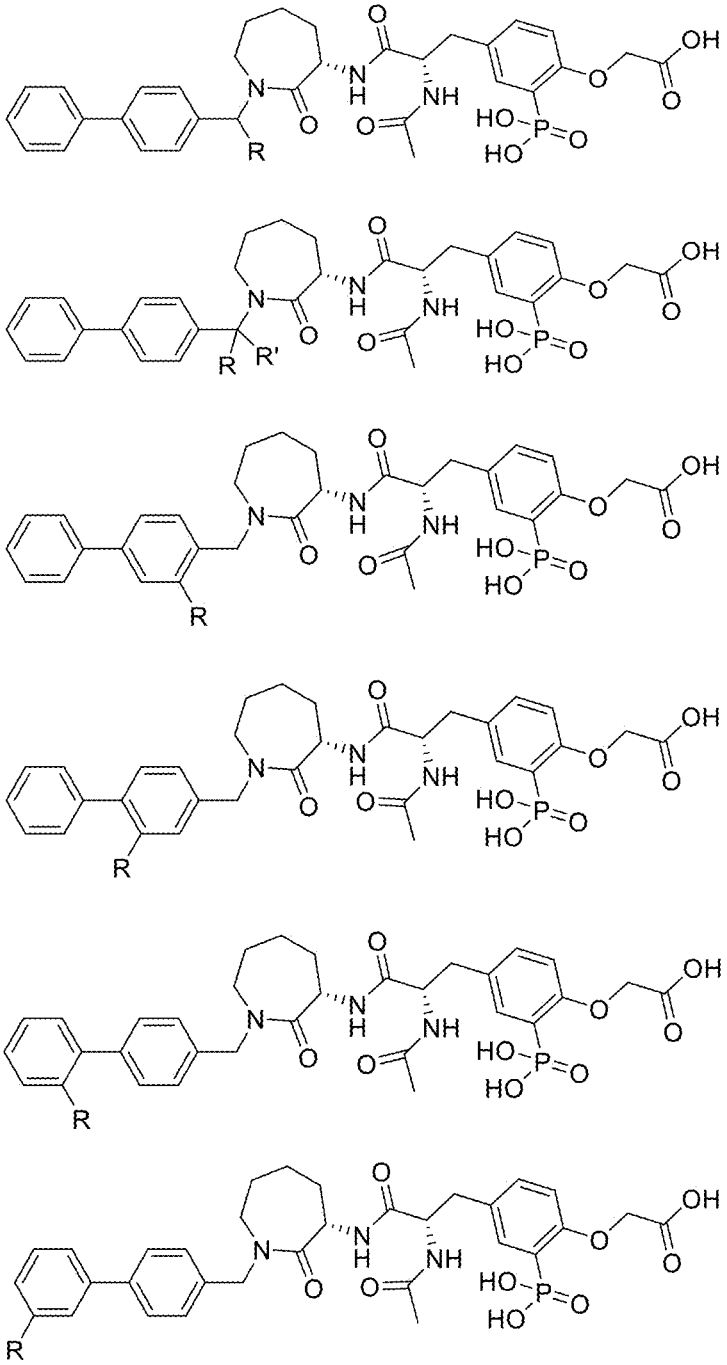


FIG. 2RRRRR

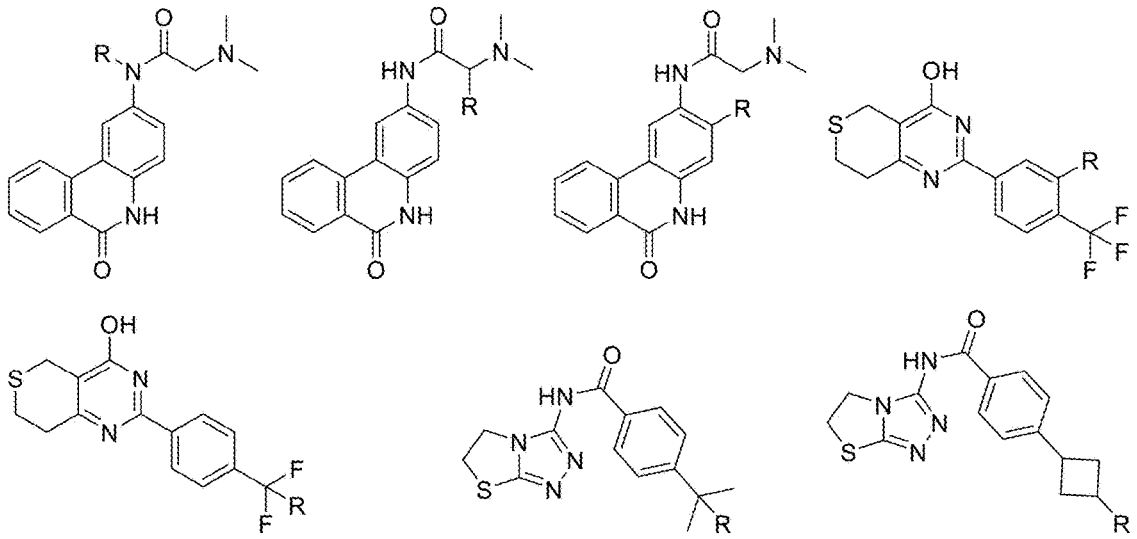


FIG. 2SSSSS

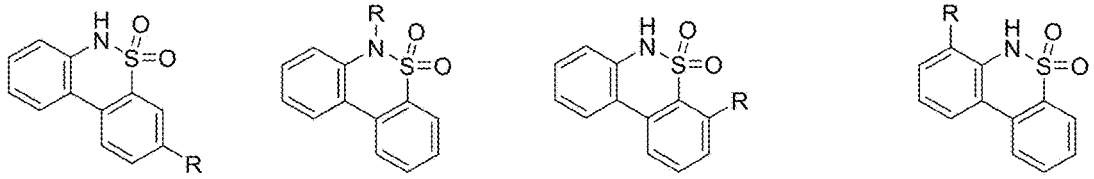


FIG. 2TTTTT

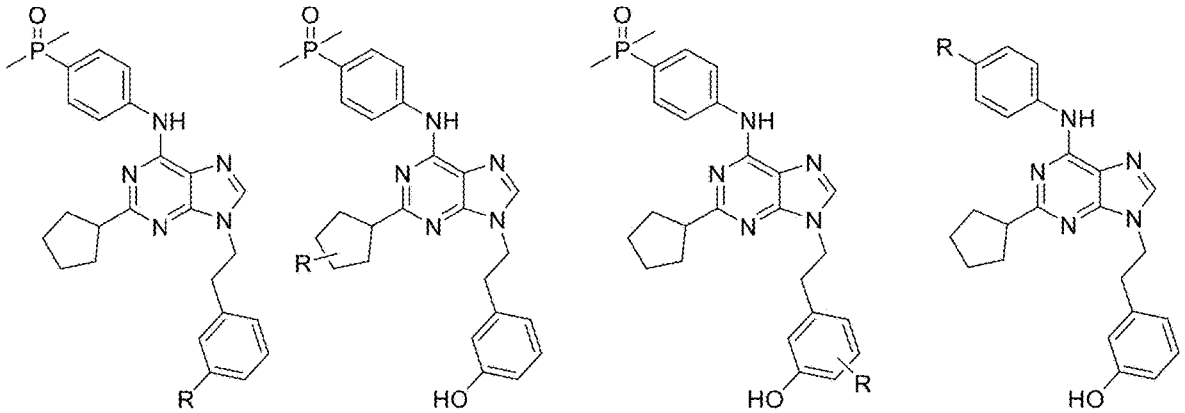


FIG. 2UUUUU

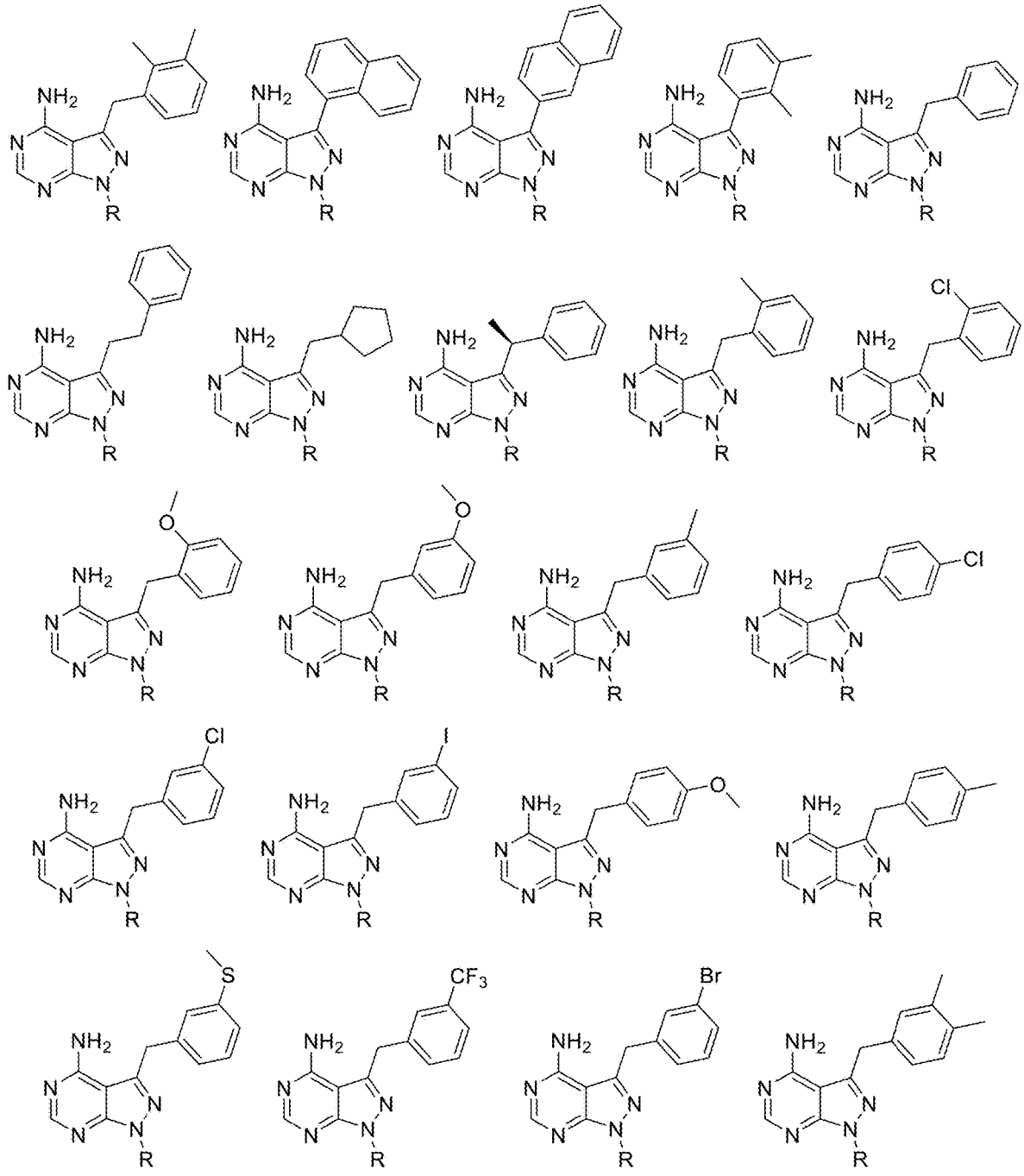


FIG. 2VVVVV

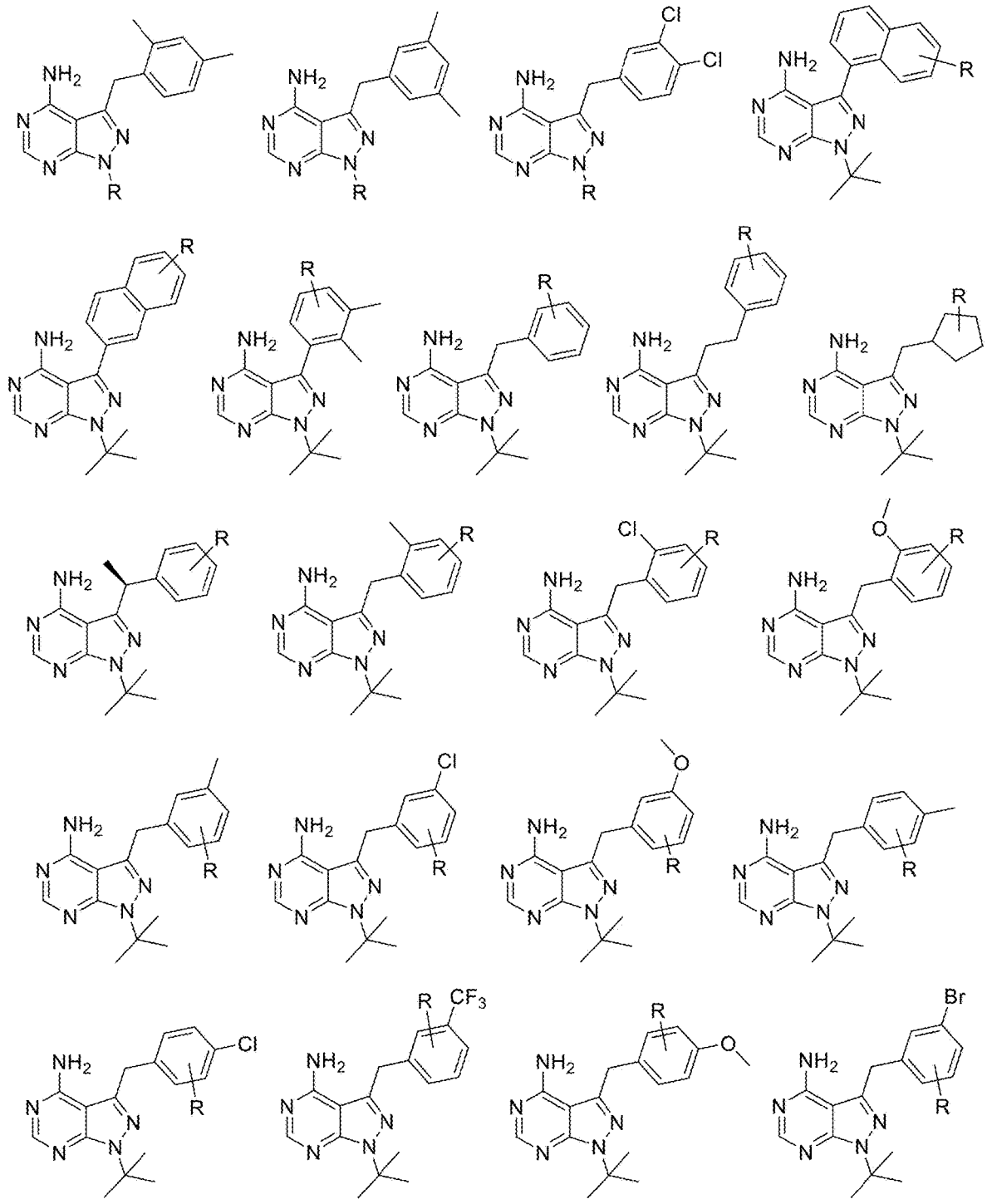


FIG. 2WWWWW

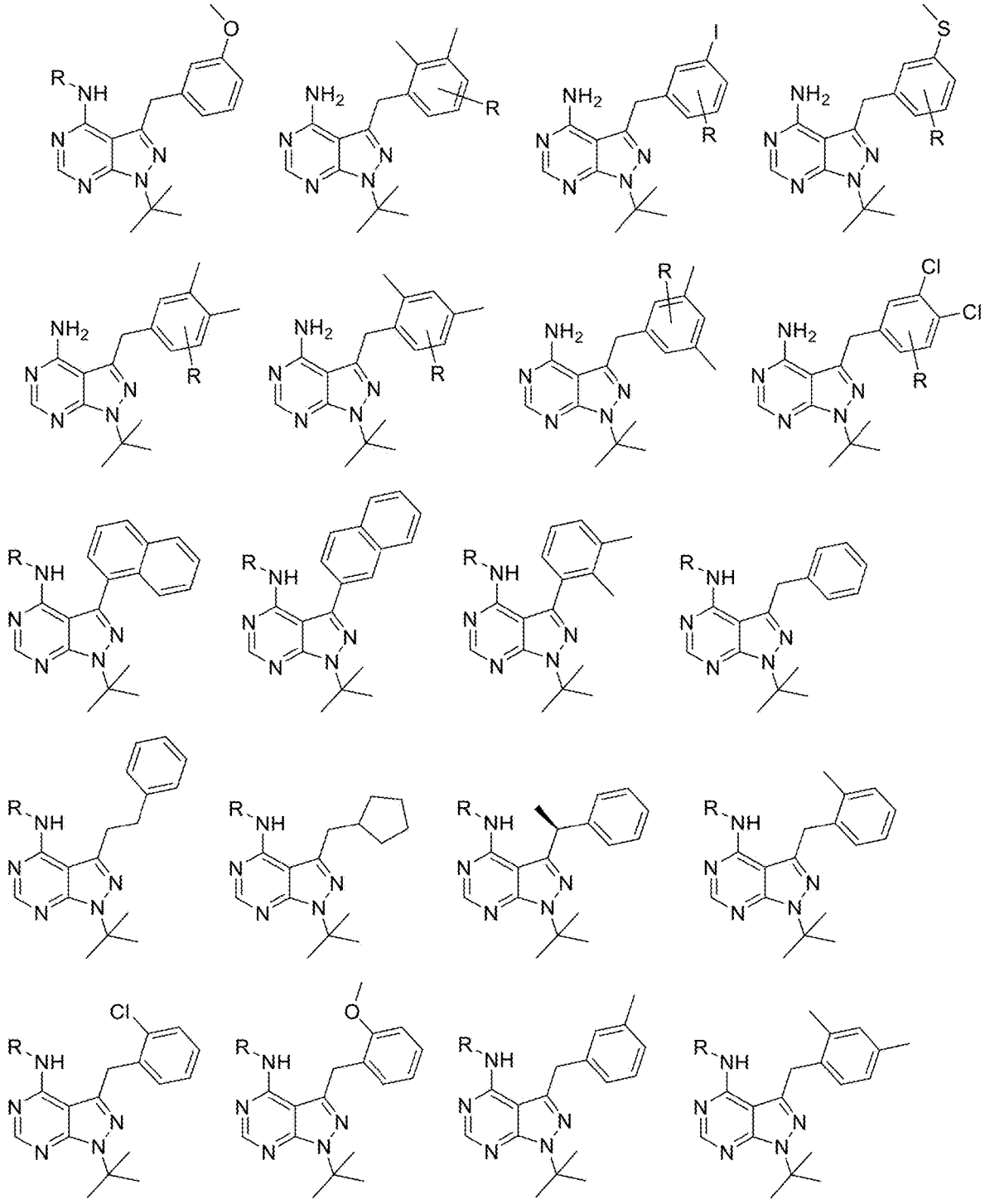


FIG. 2XXXXX

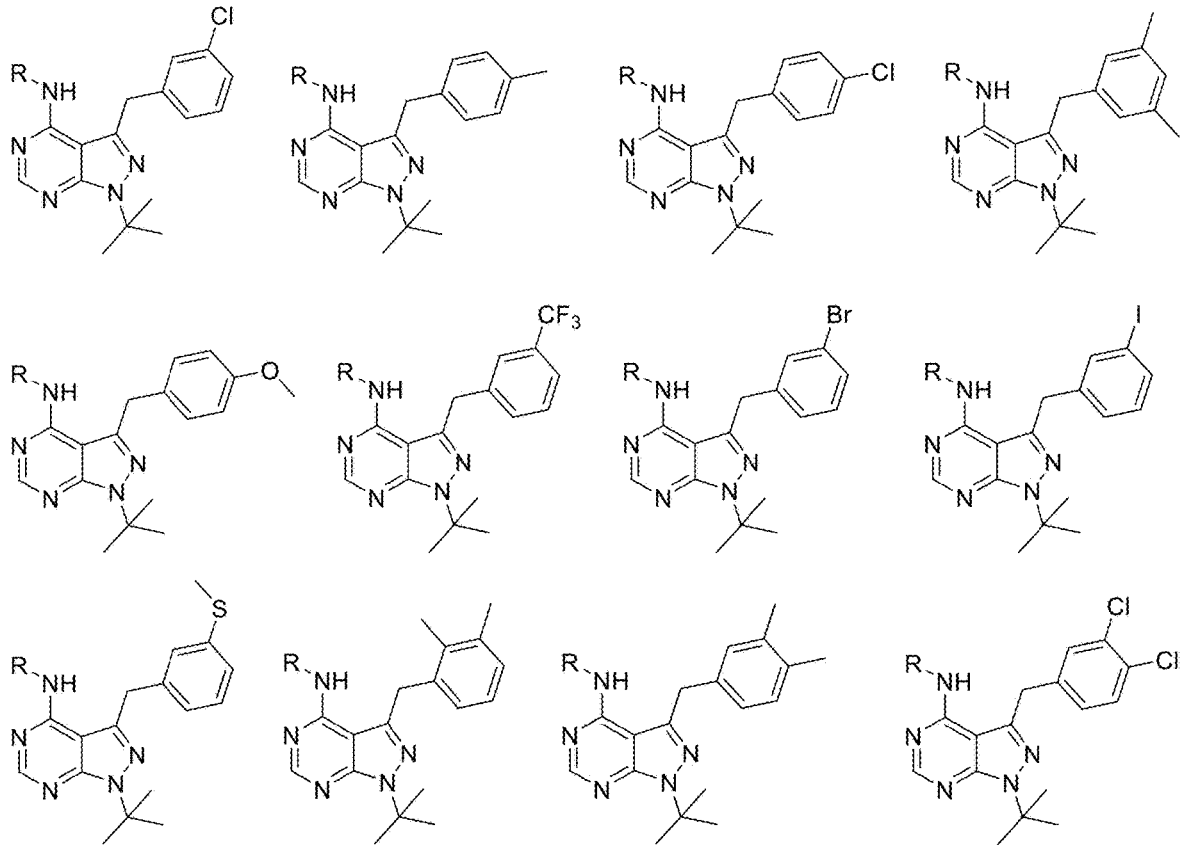


FIG. 2YYYYY

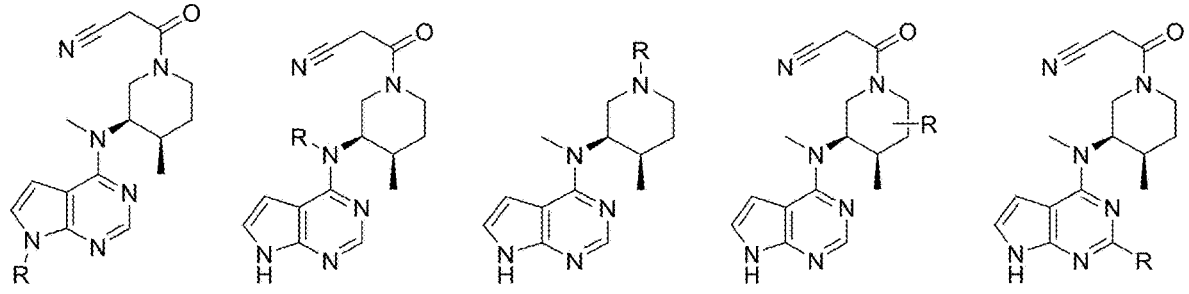


FIG. 2ZZZZZ

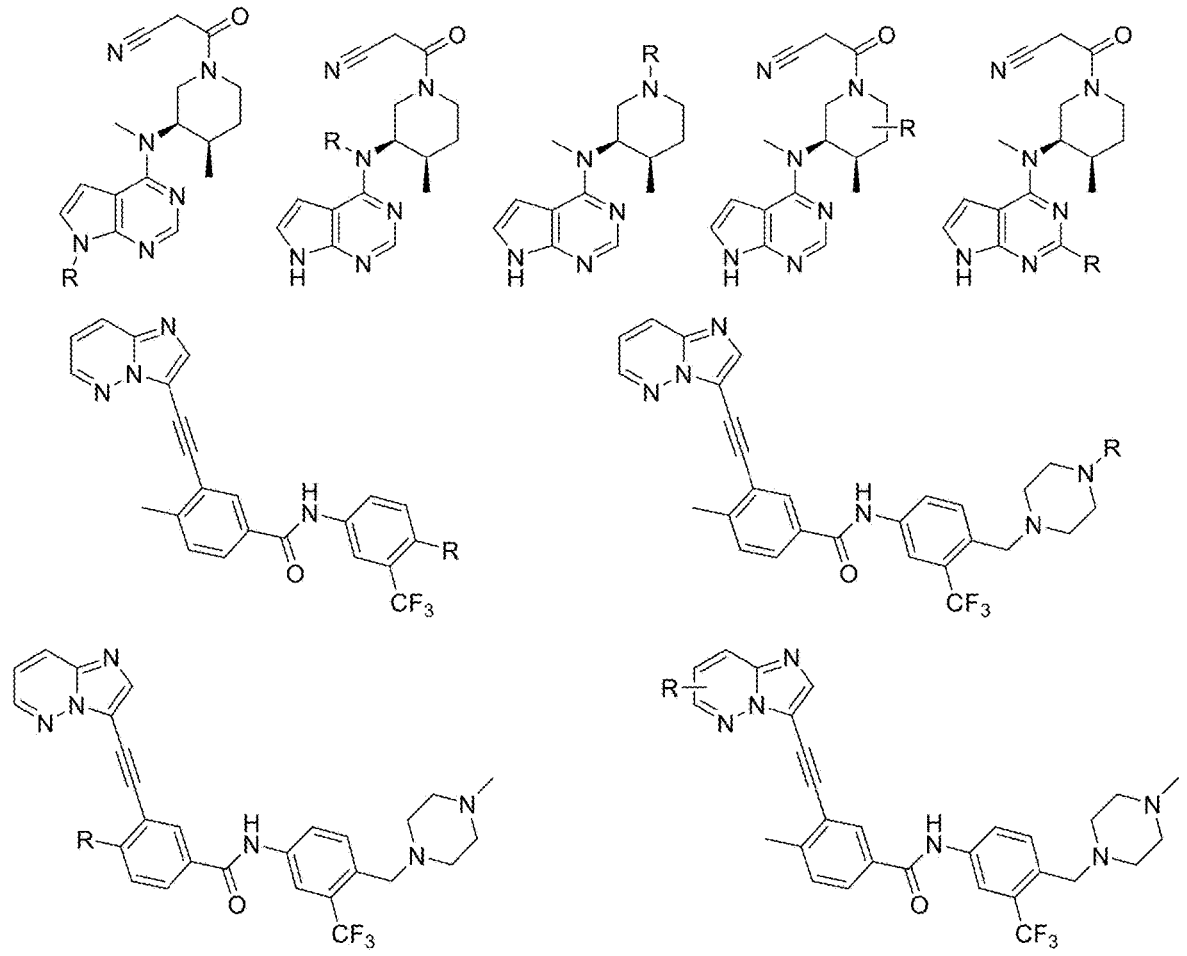


FIG. 3A

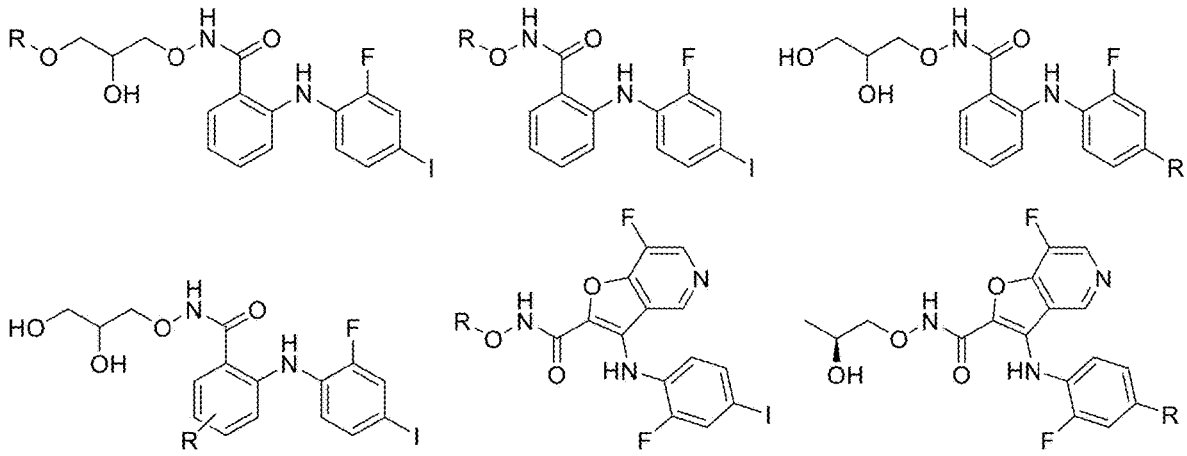


FIG. 3B

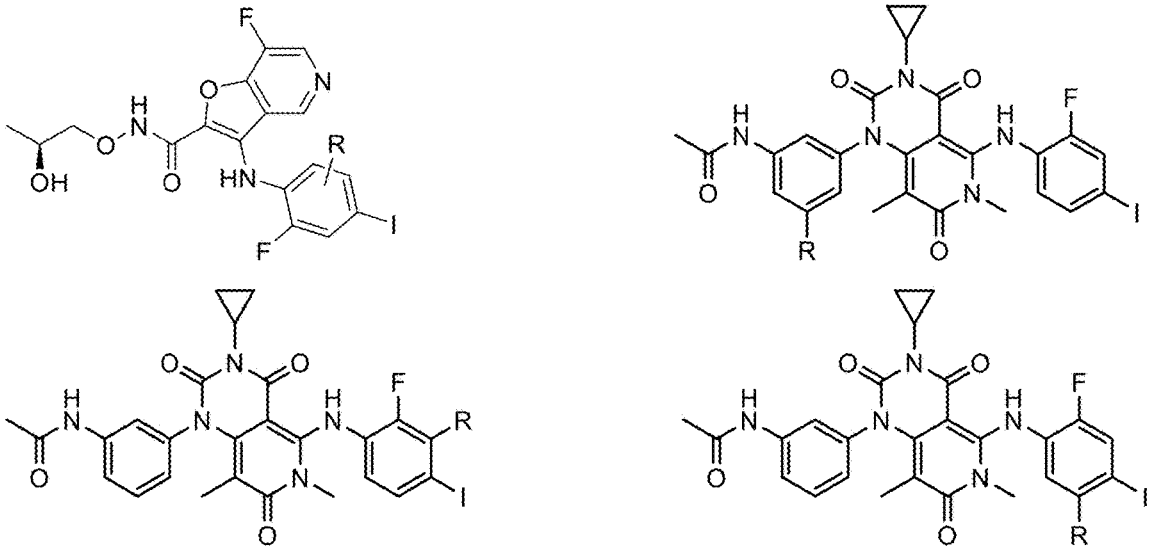


FIG. 3C

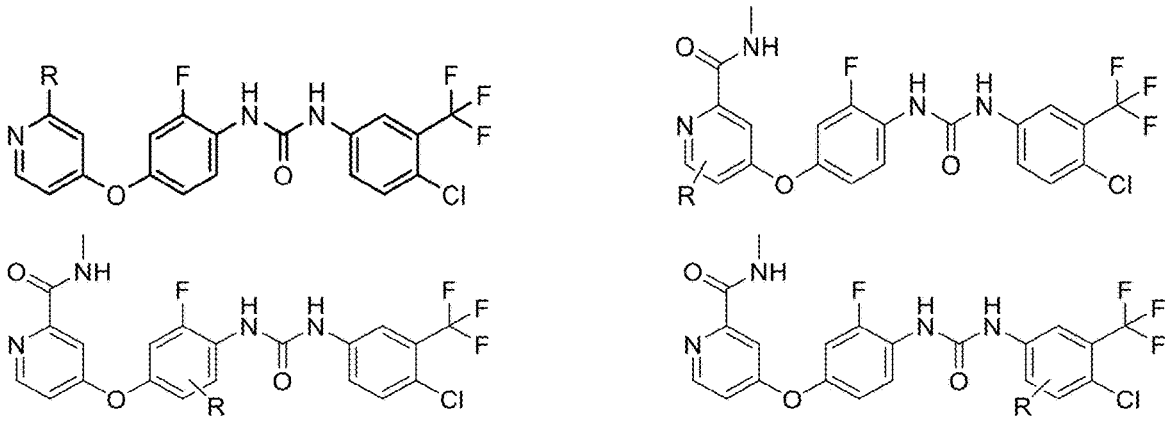


FIG. 3D

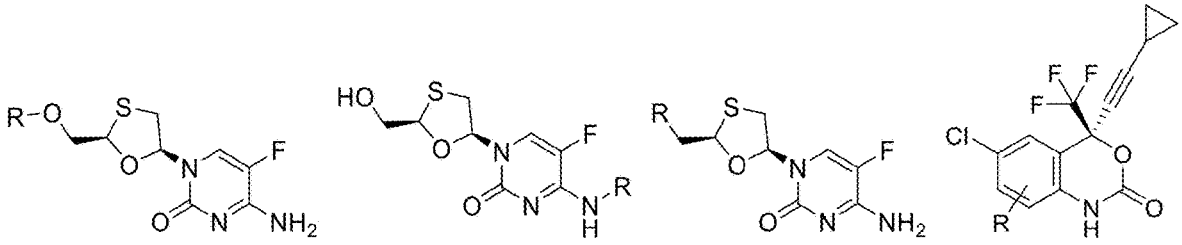


FIG. 3E

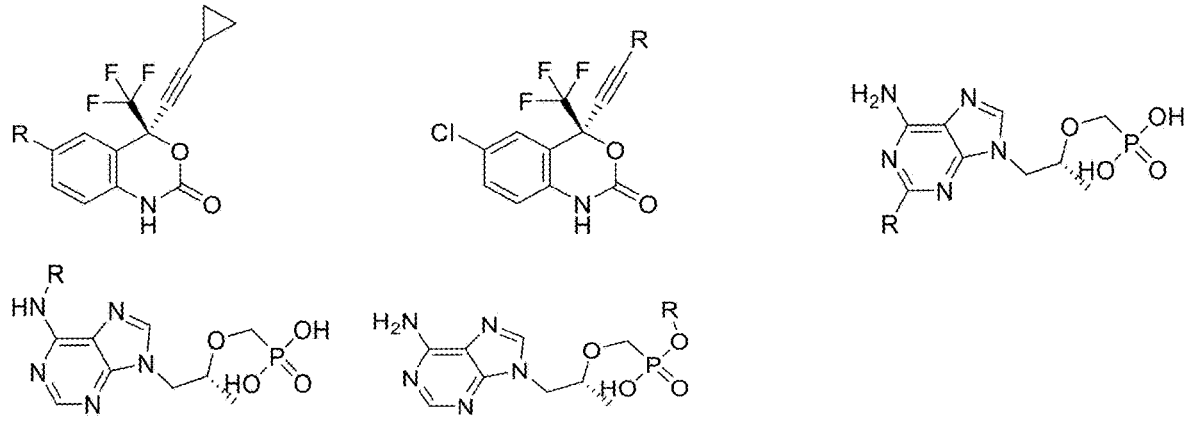


FIG. 3F

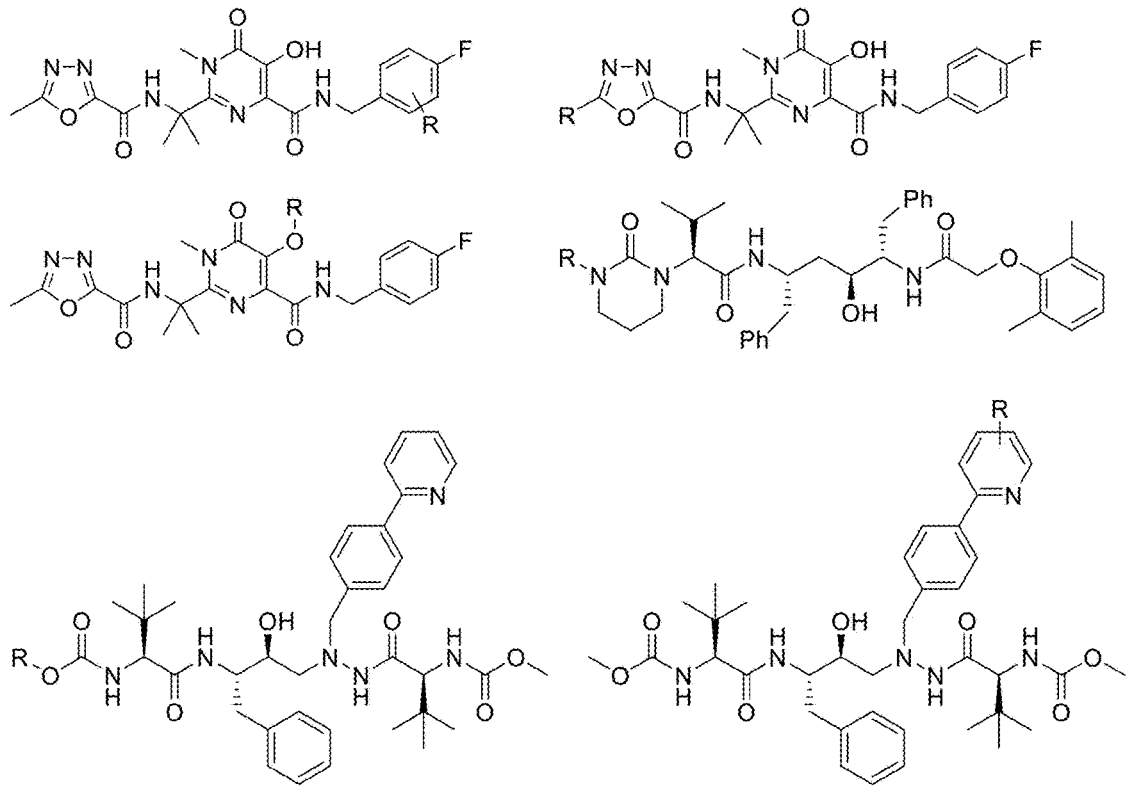


FIG. 3G

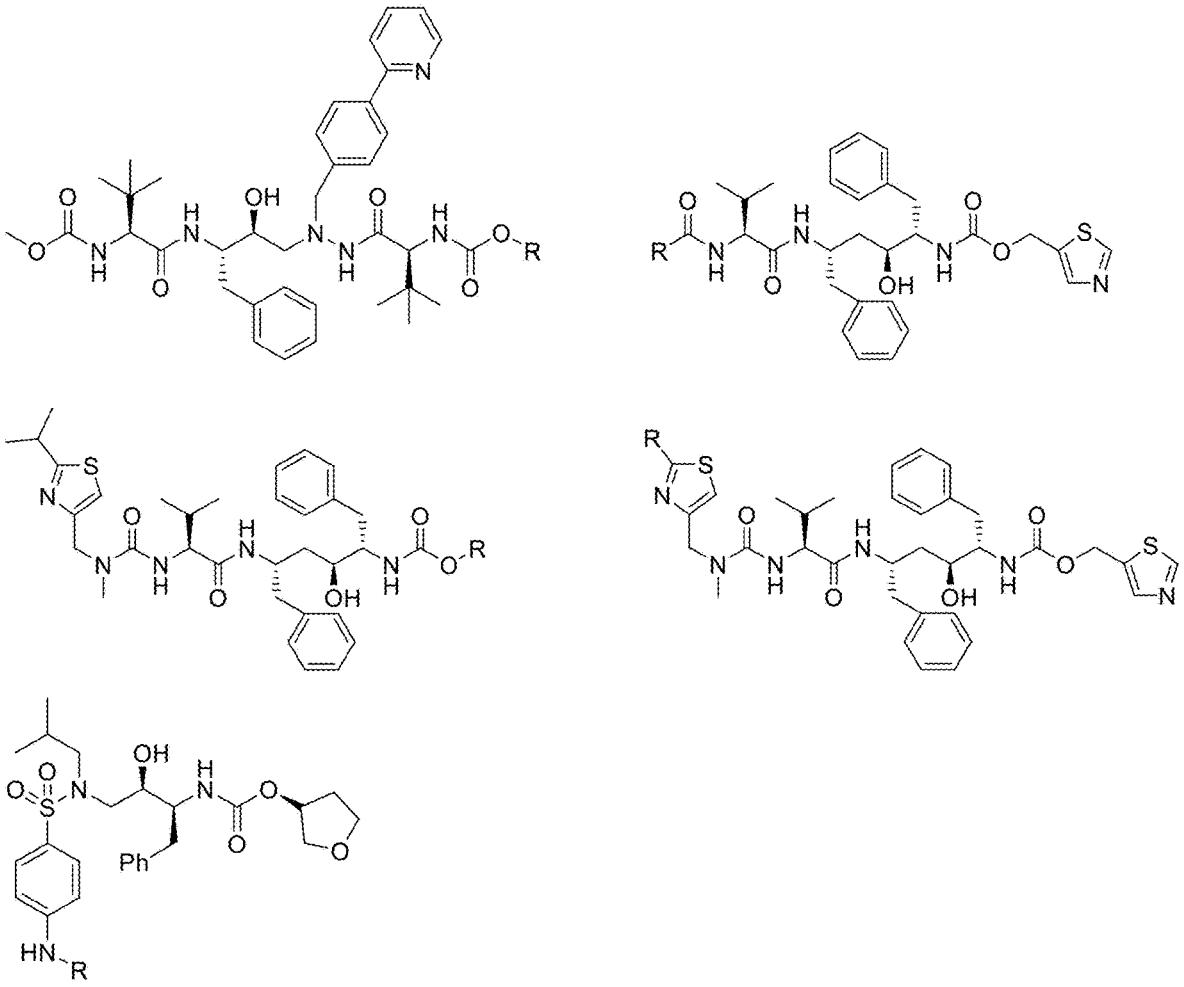


FIG. 3H

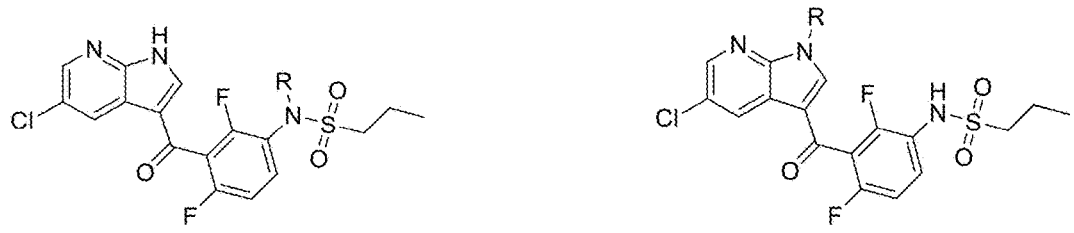
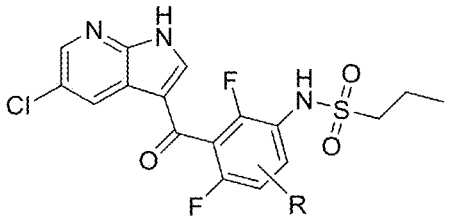


FIG. 3I



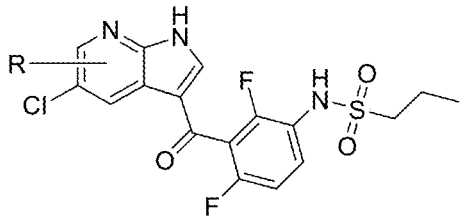
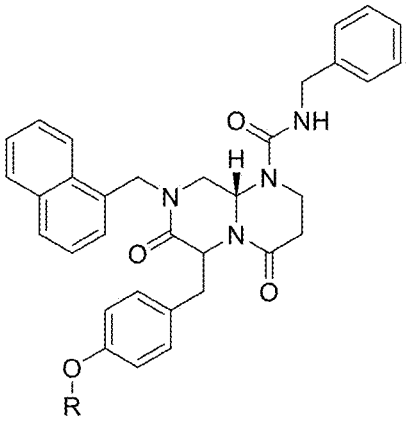
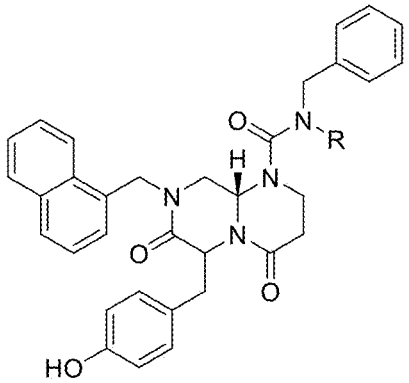
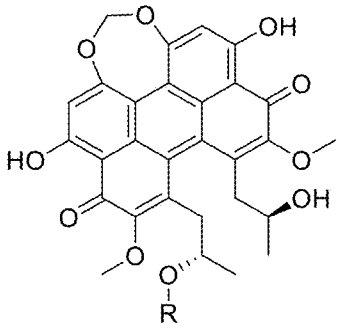
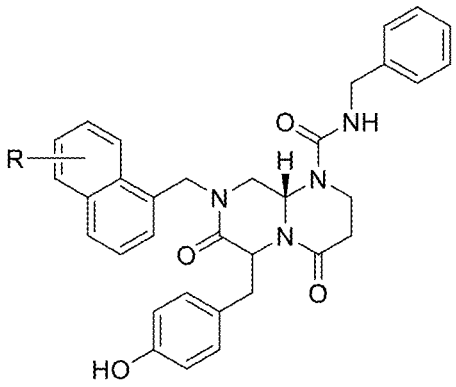


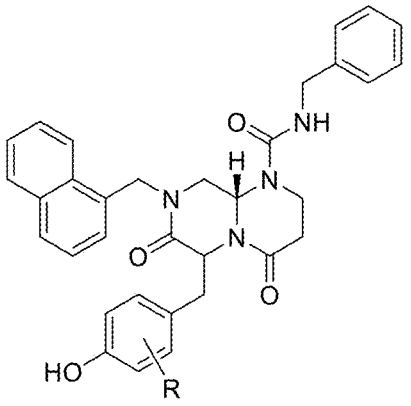
FIG. 3J

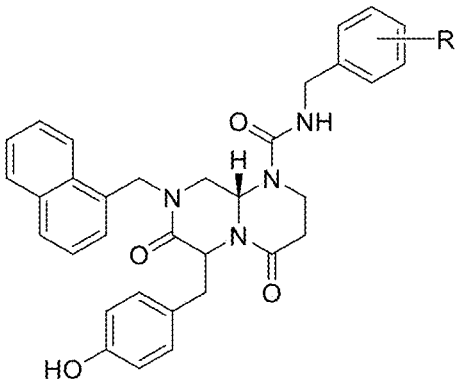












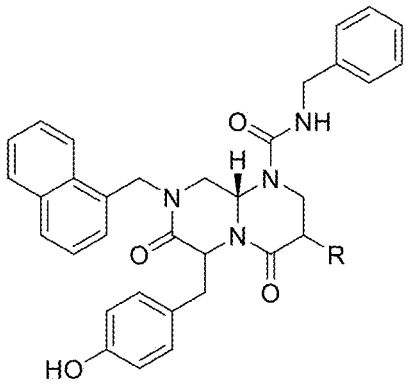


FIG. 3K

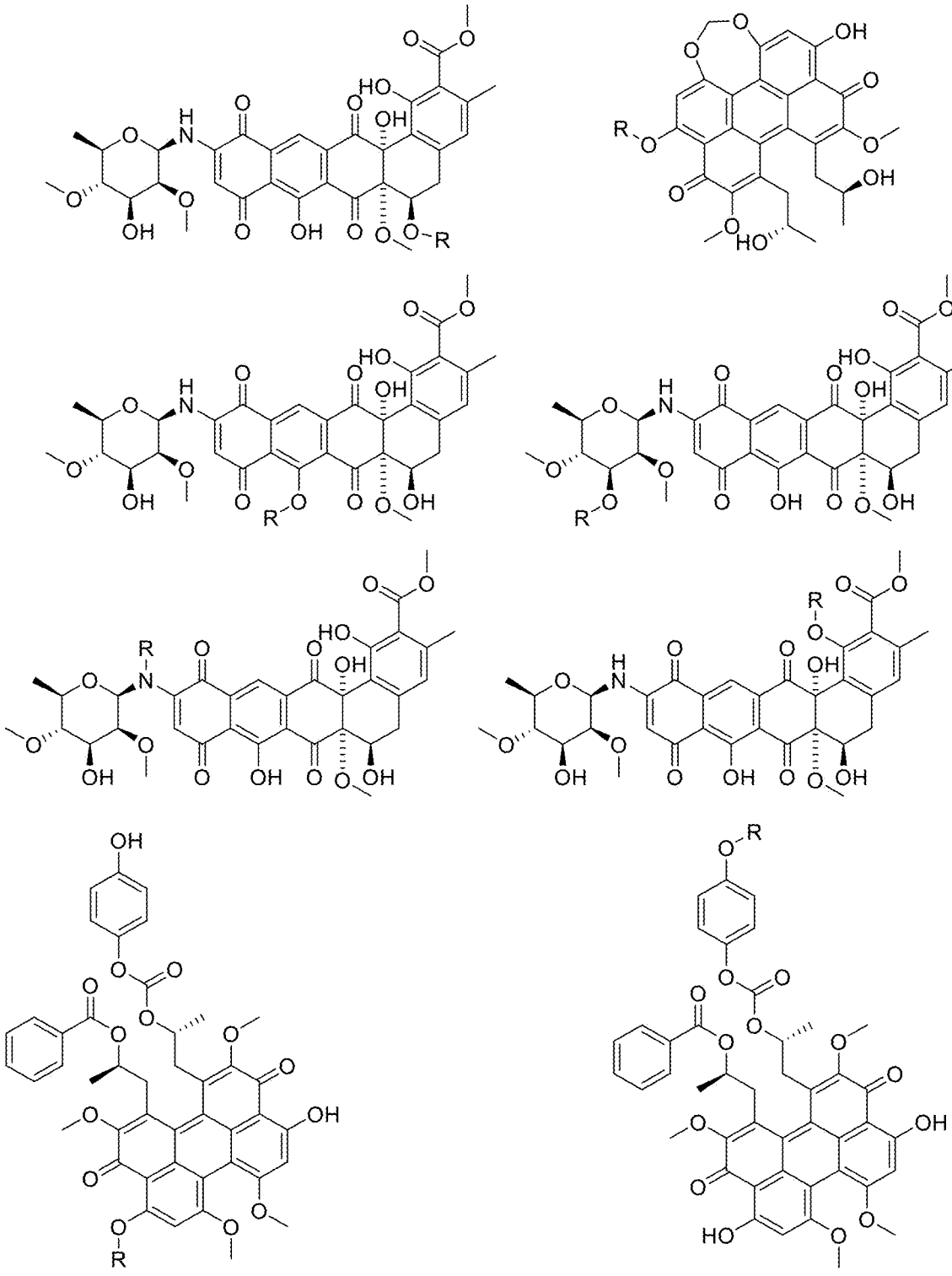


FIG. 3L

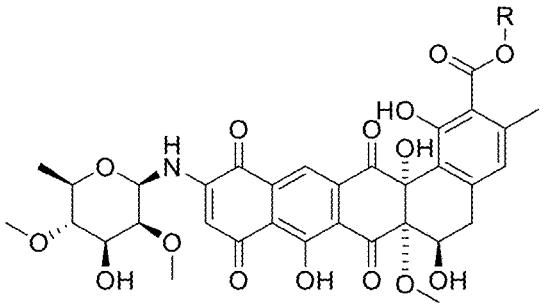


FIG. 3M

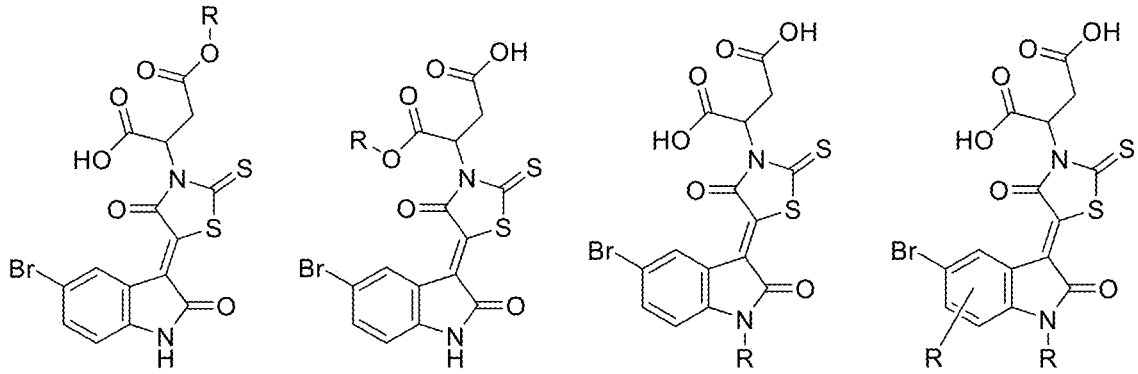


FIG. 3N

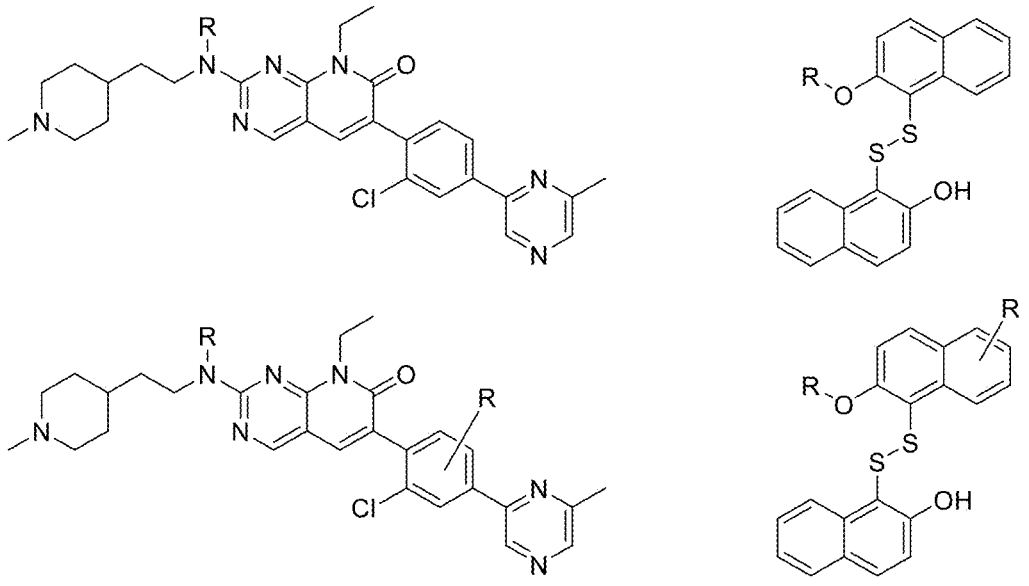


FIG. 3O

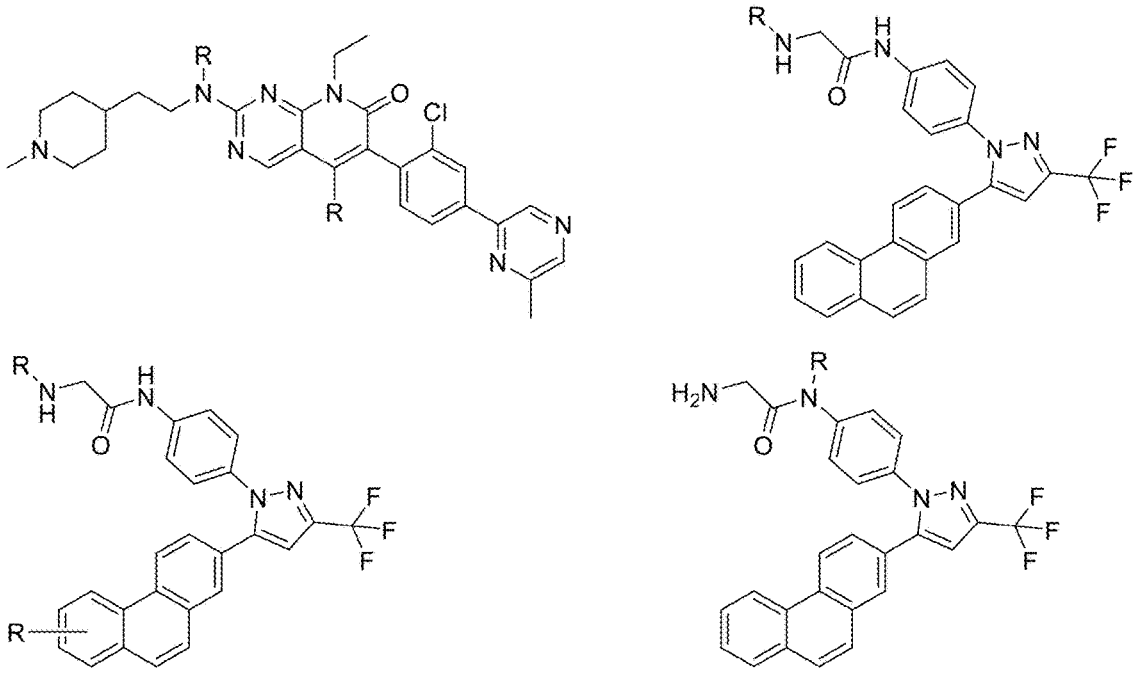


FIG. 3P

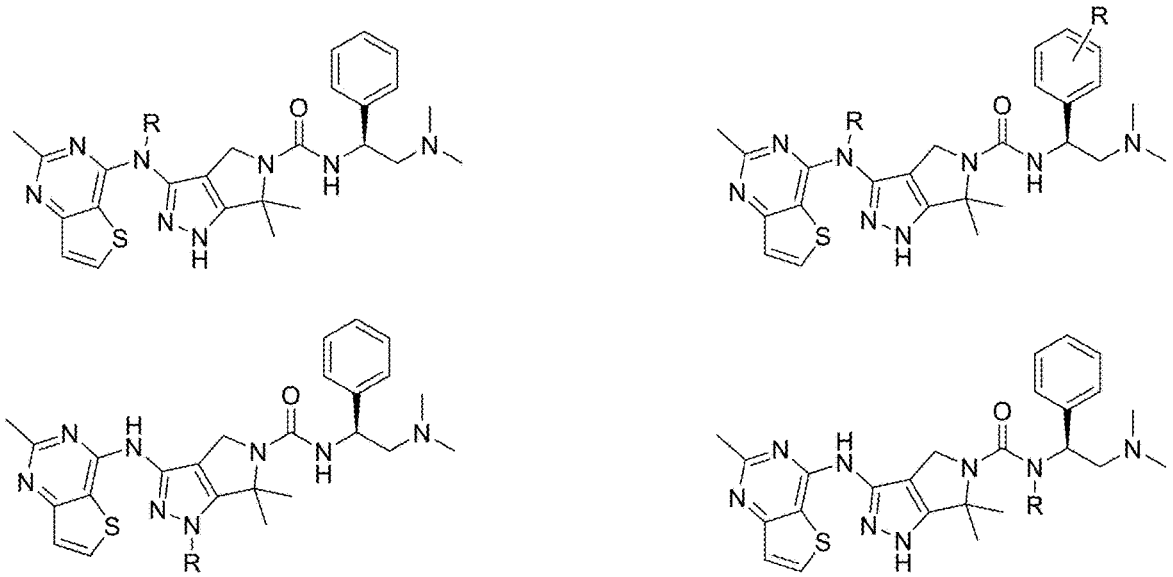


FIG. 3Q

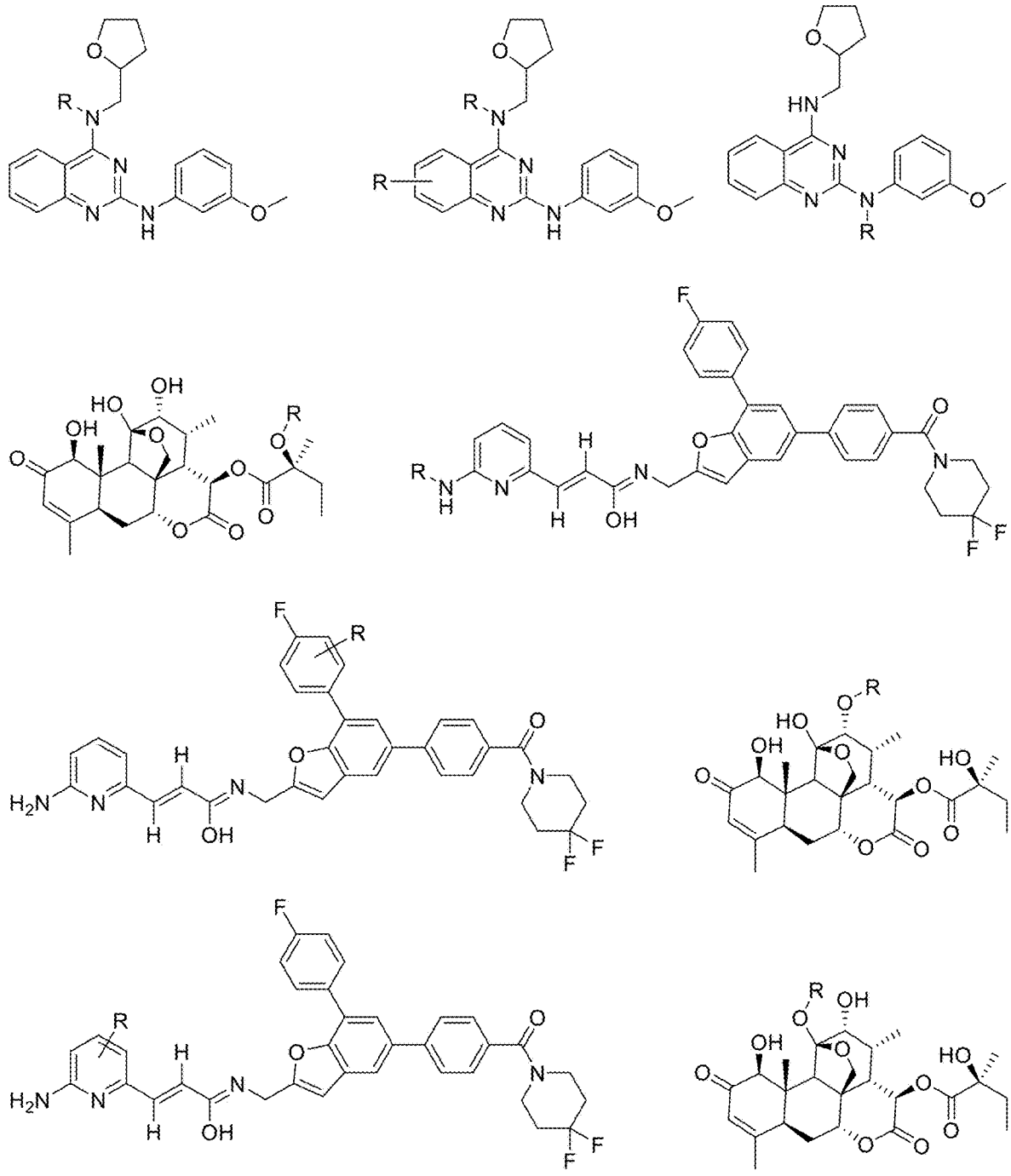


FIG. 3R

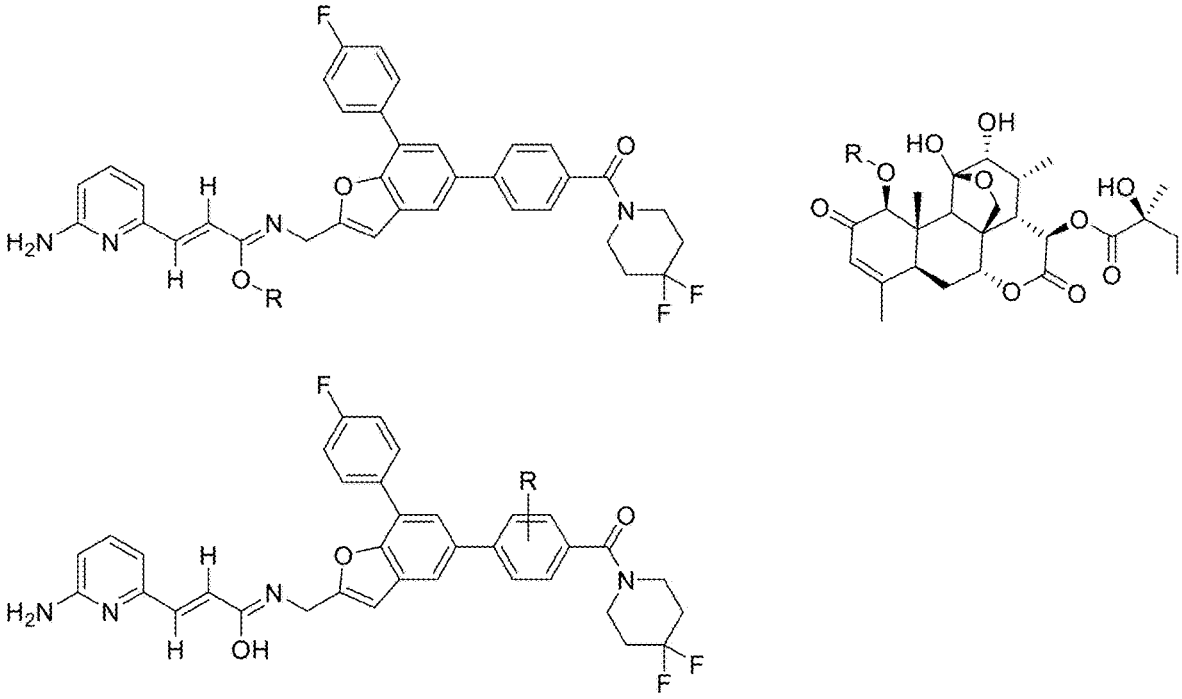


FIG. 3S

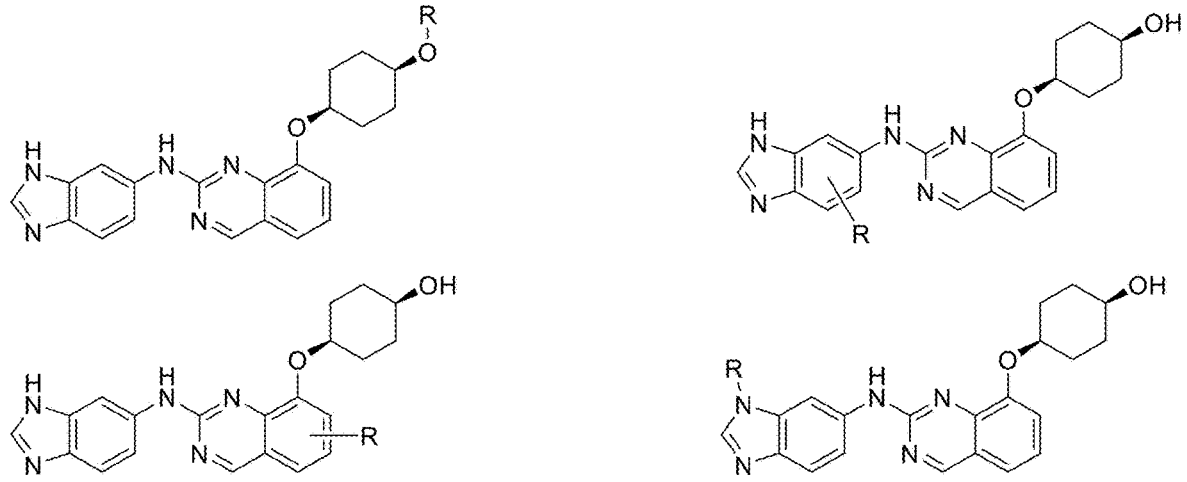


FIG. 3T

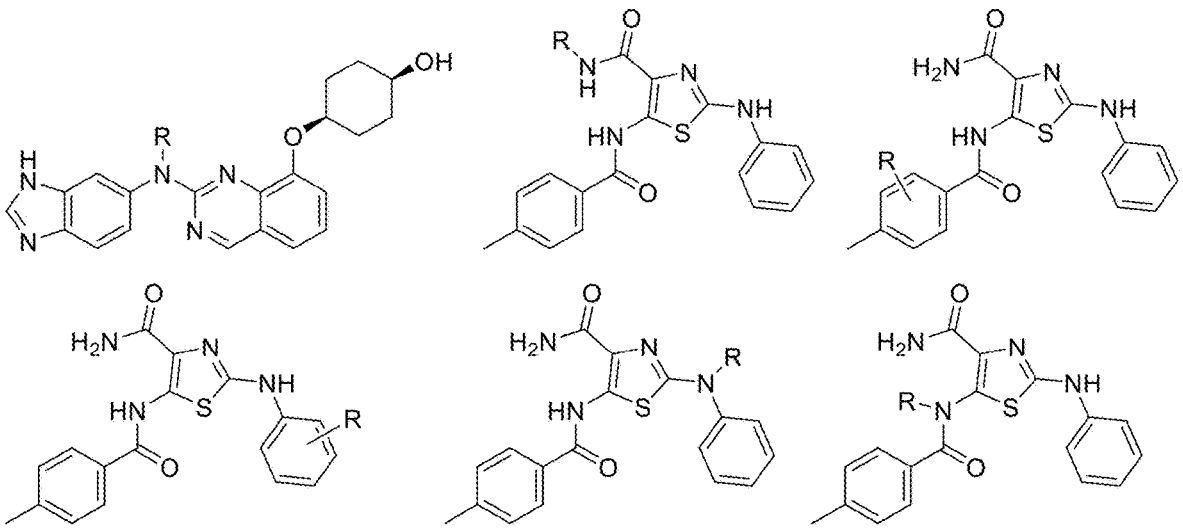


FIG. 3U

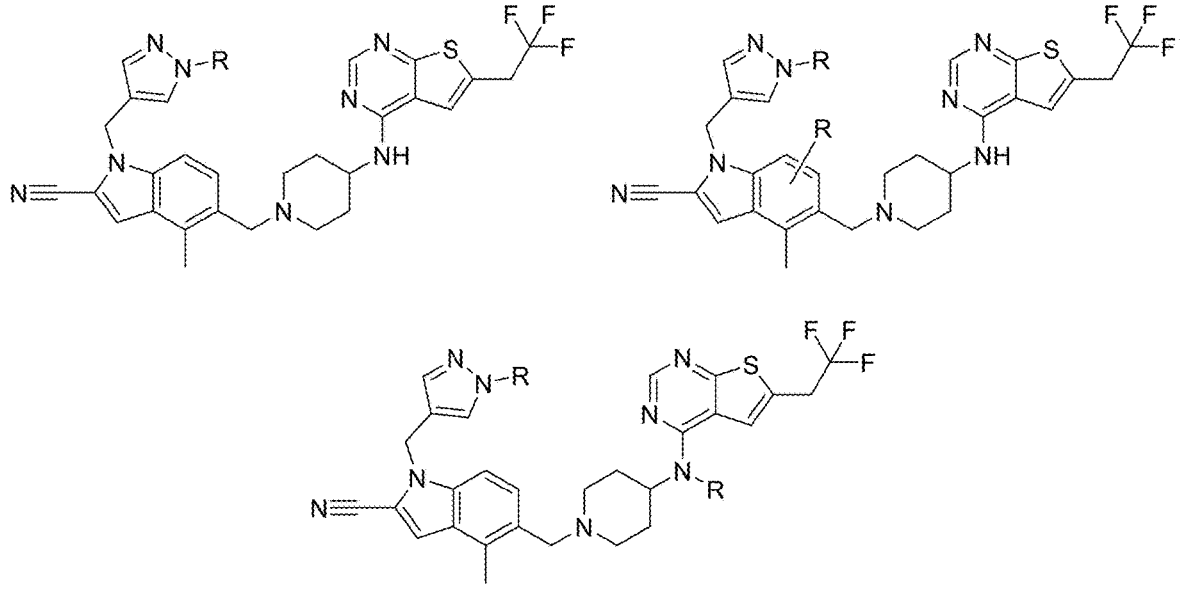


FIG. 3V

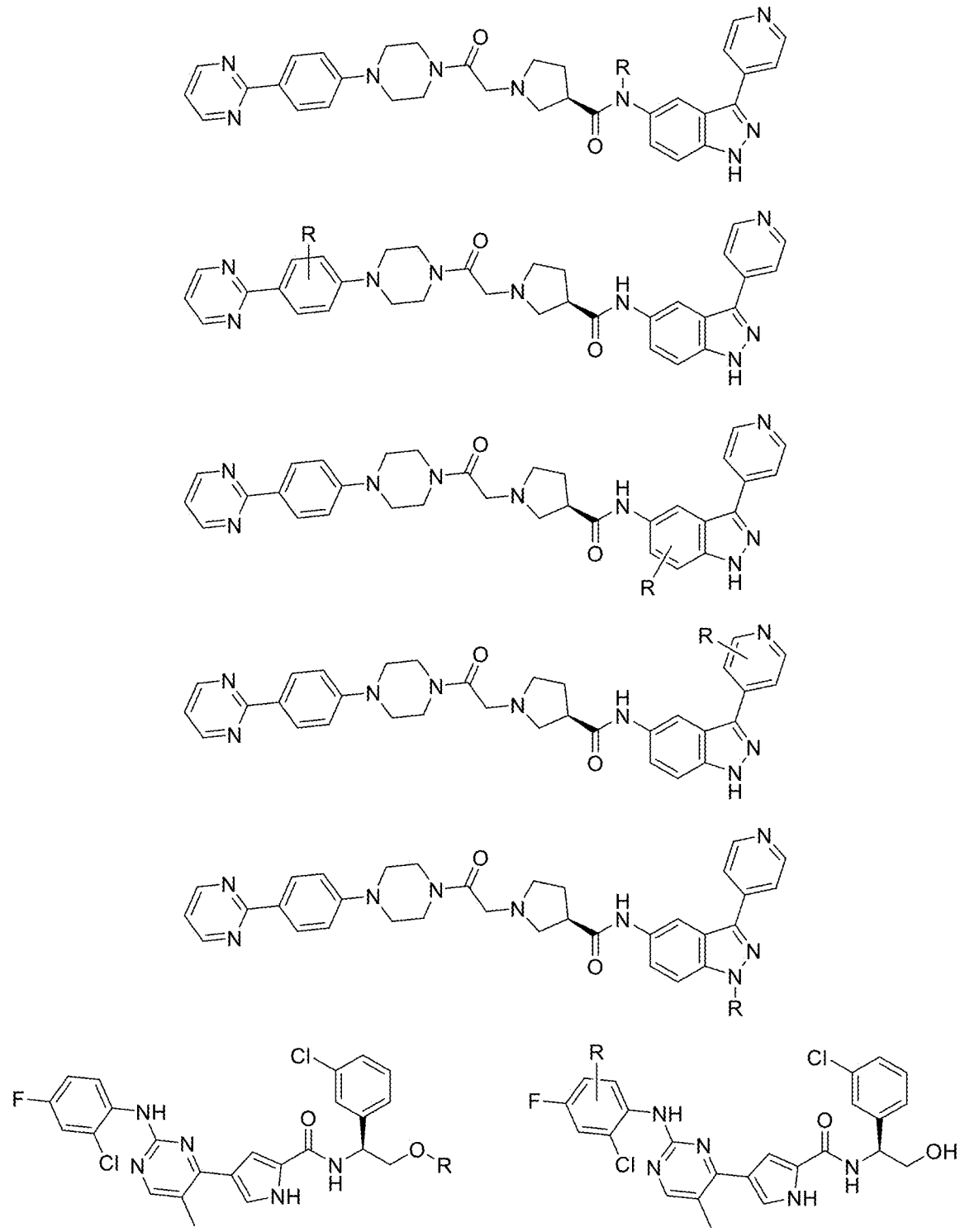


FIG. 3W

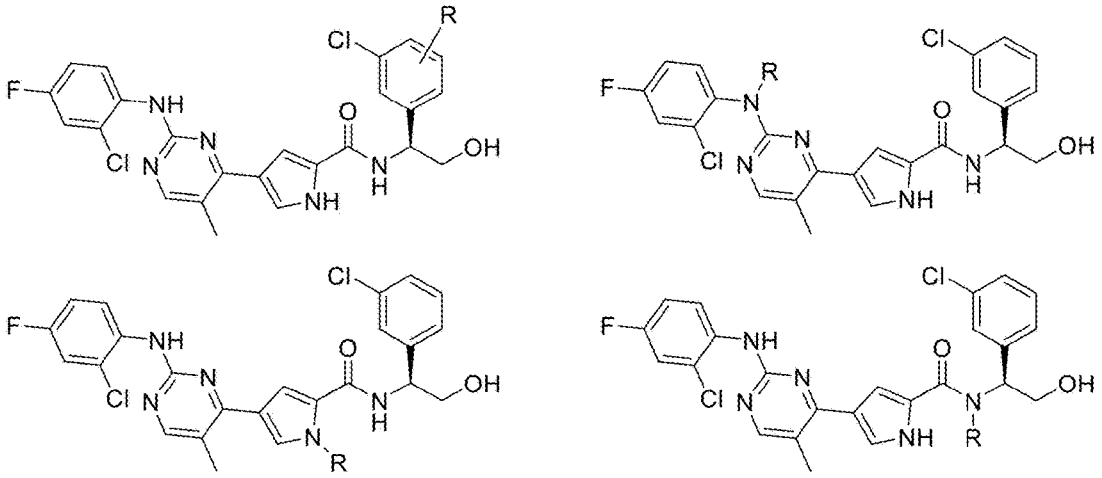


FIG. 3X

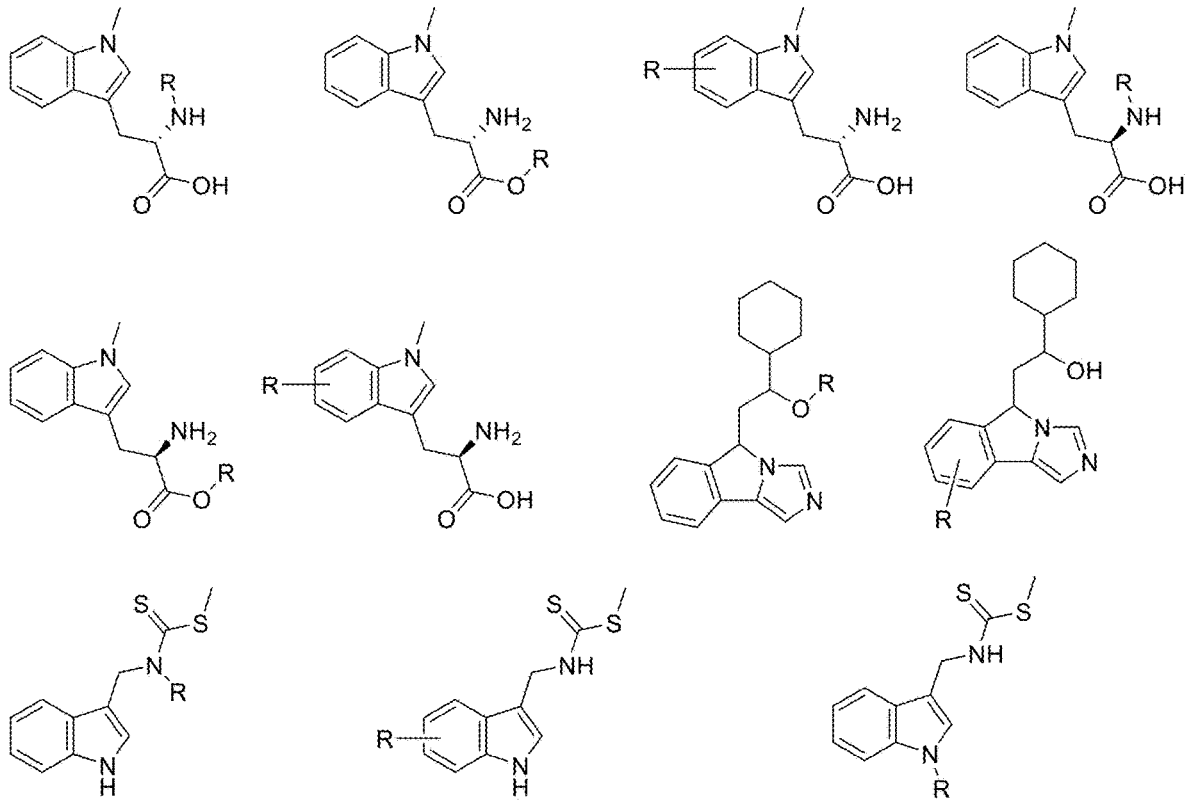


FIG. 3Y

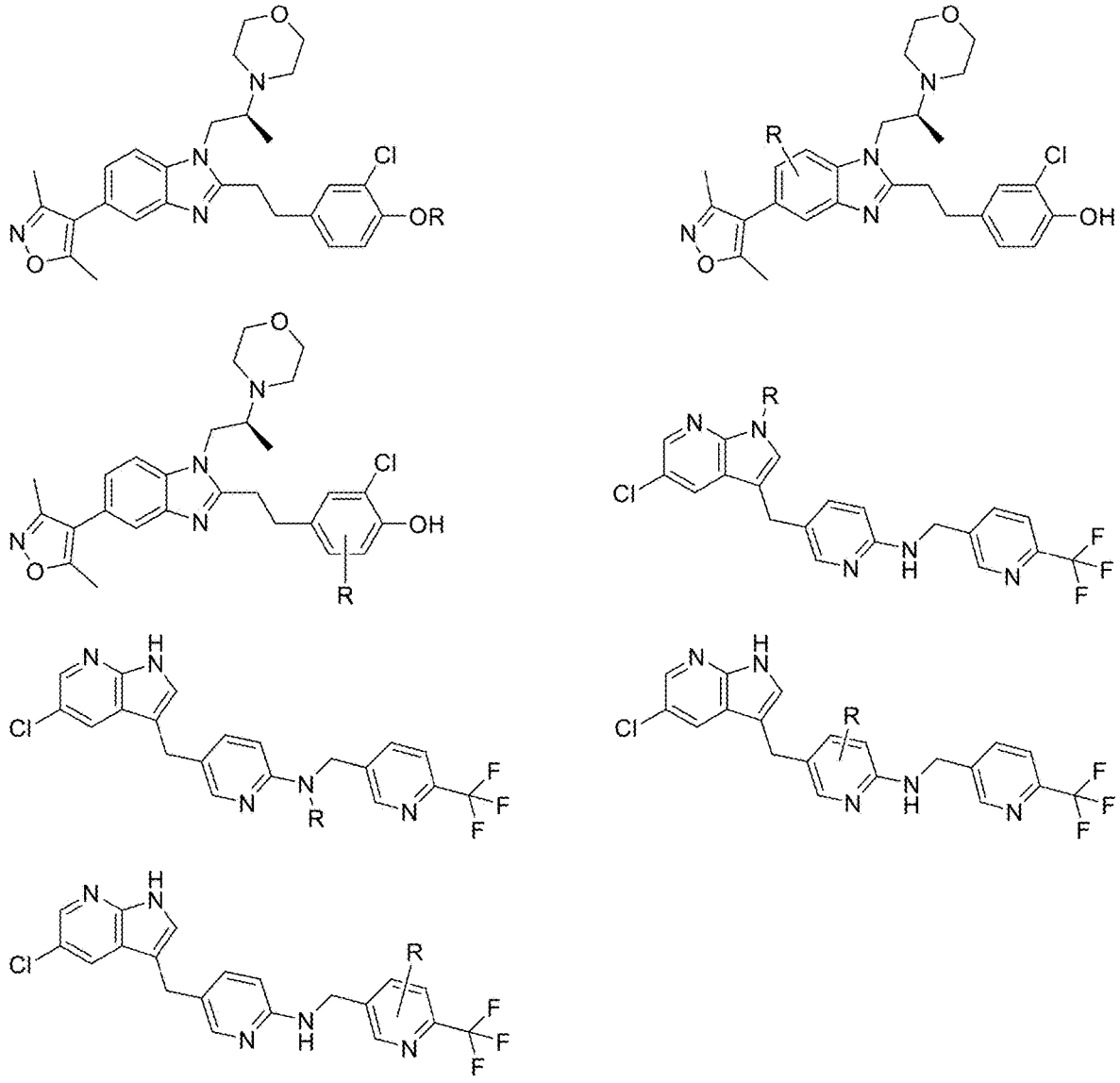


FIG. 3Z

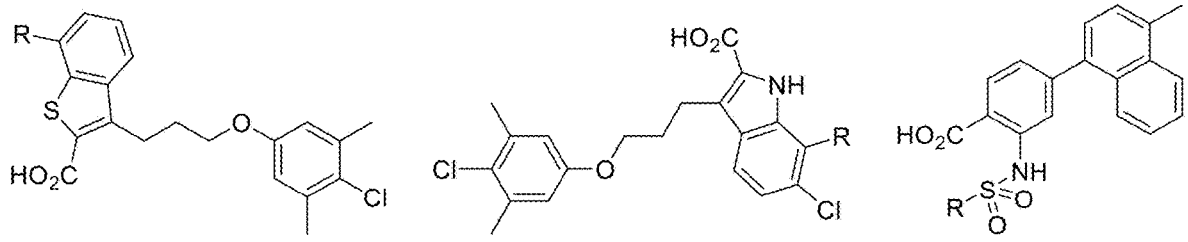


FIG. 3AA

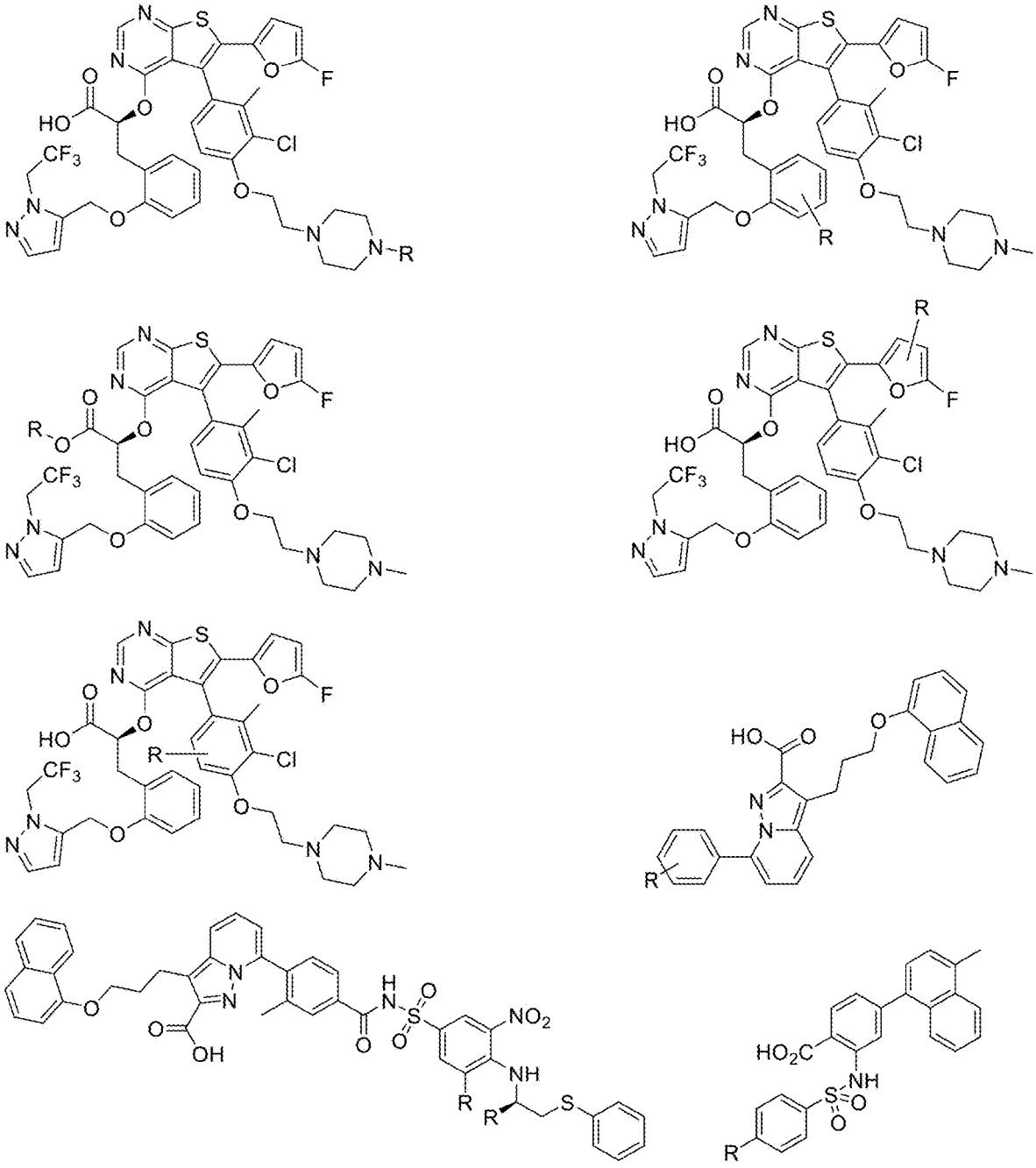


FIG. 3BB

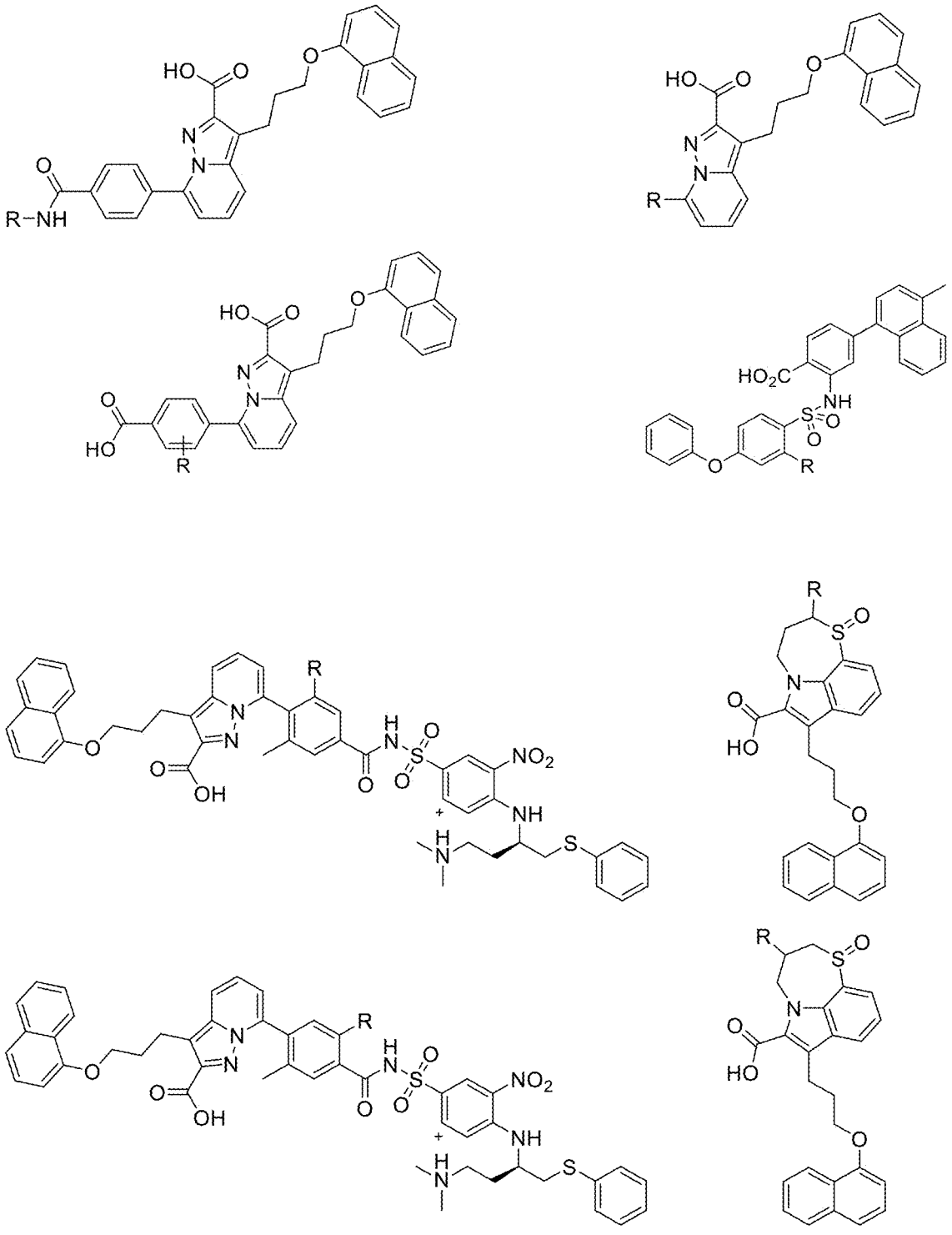


FIG. 3CC

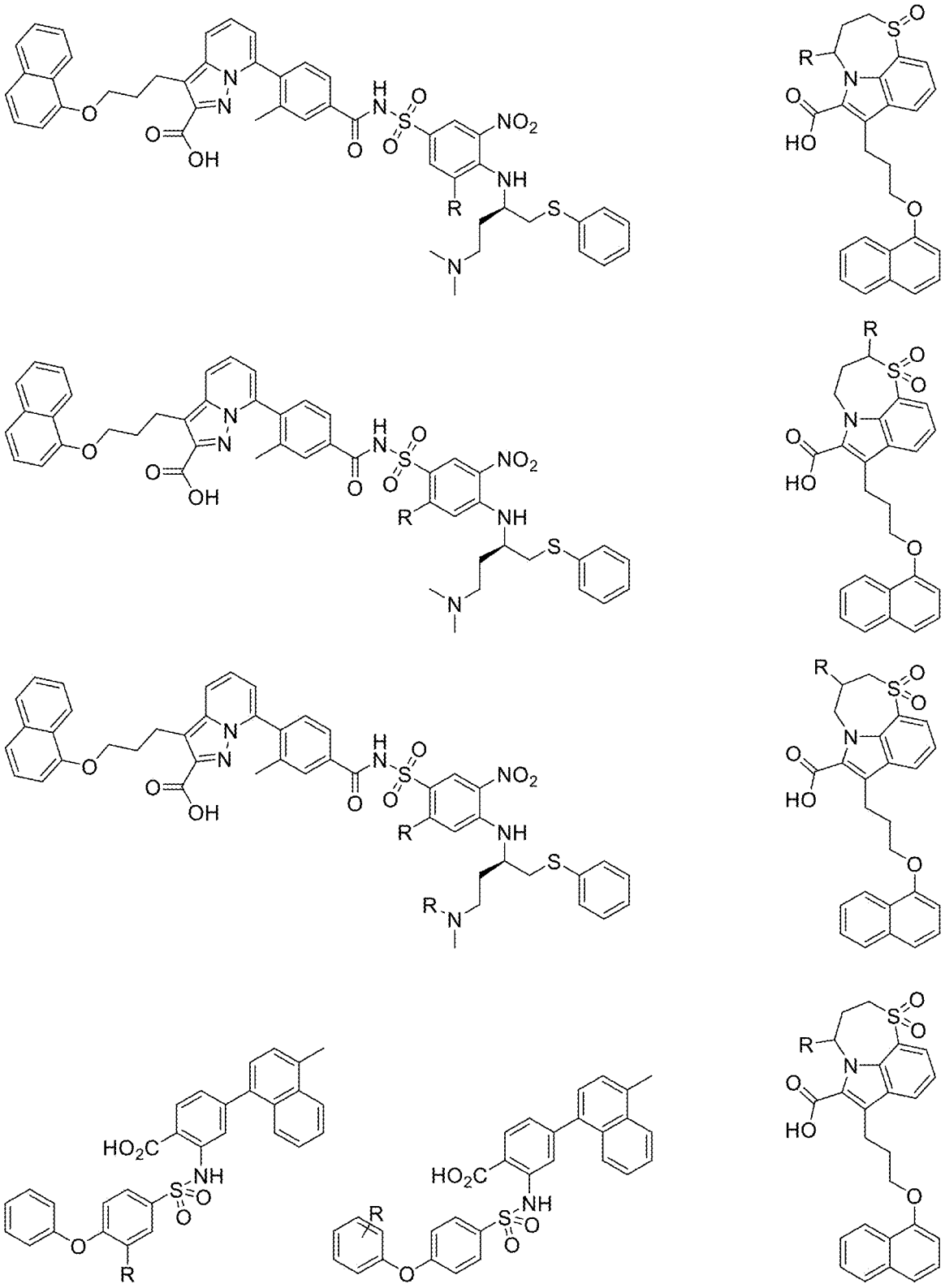


FIG. 3DD

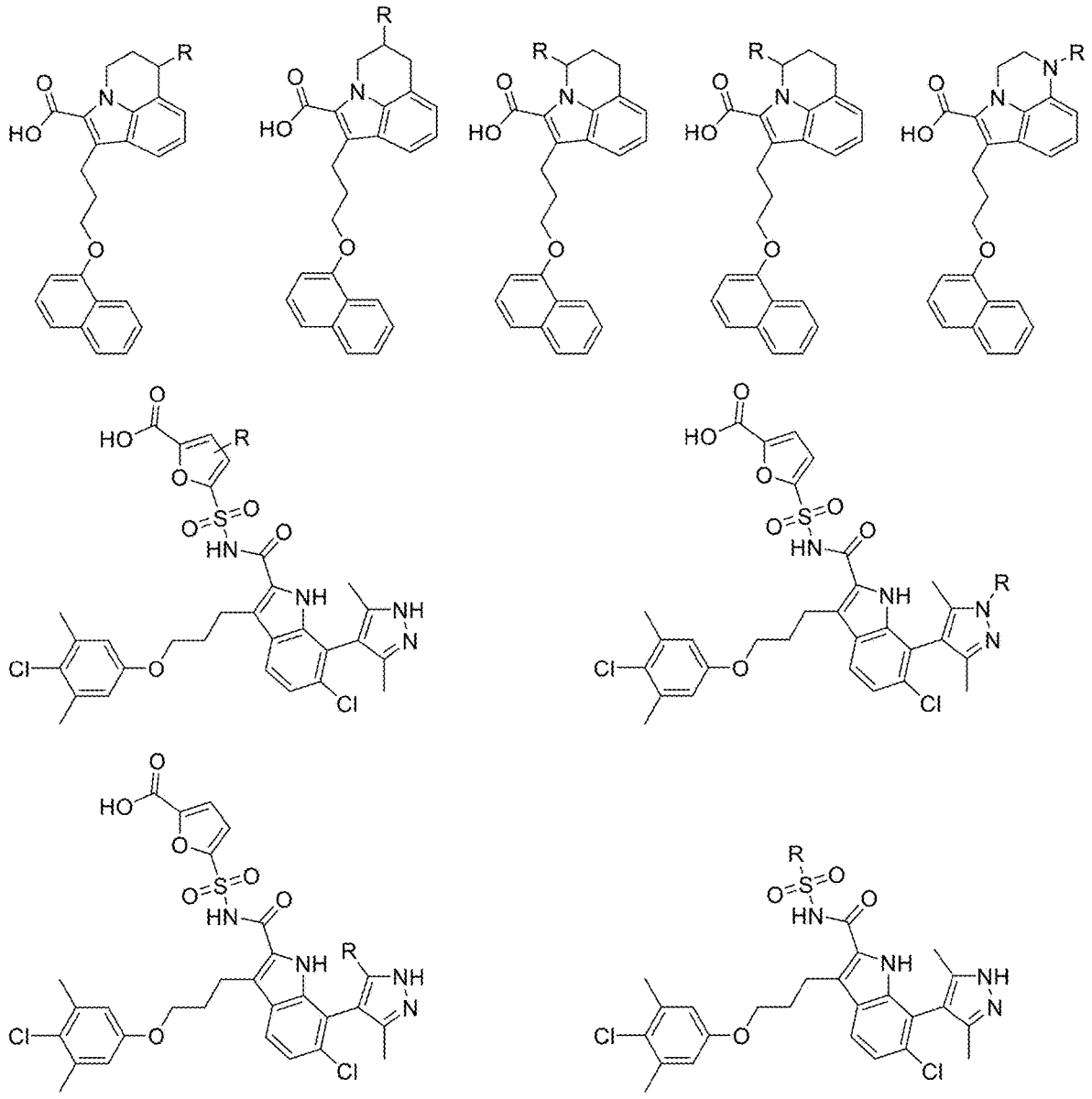


FIG. 3EE

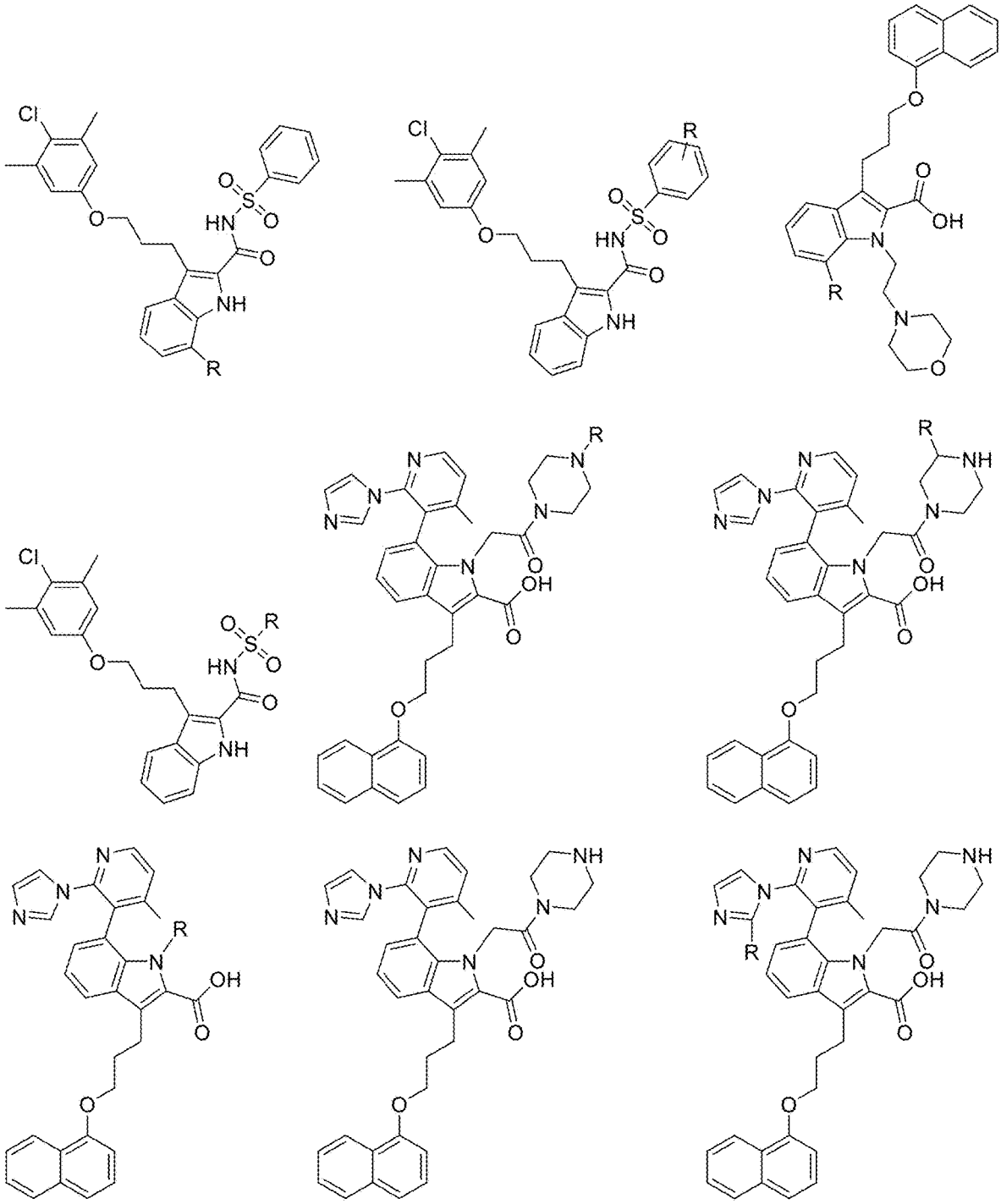


FIG. 3FF

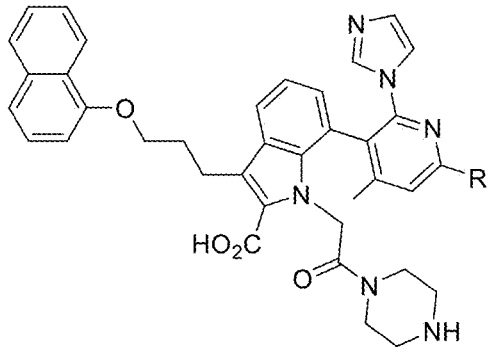
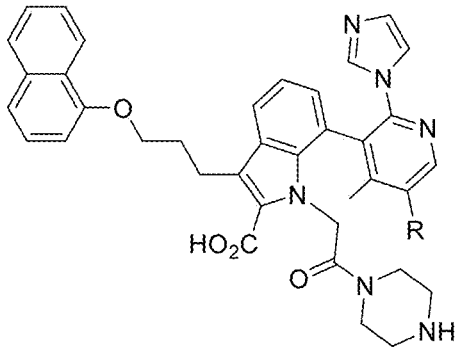
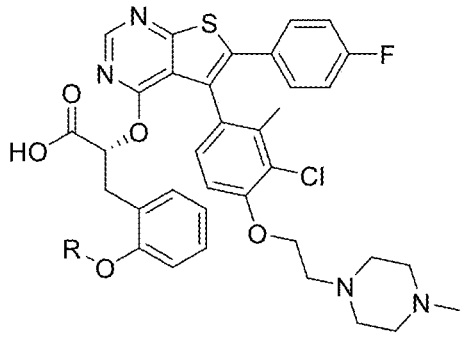
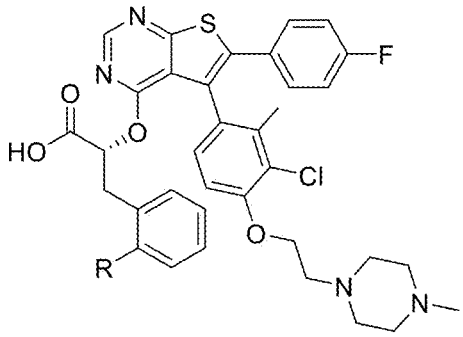
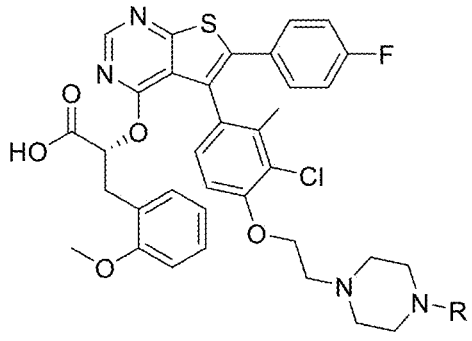
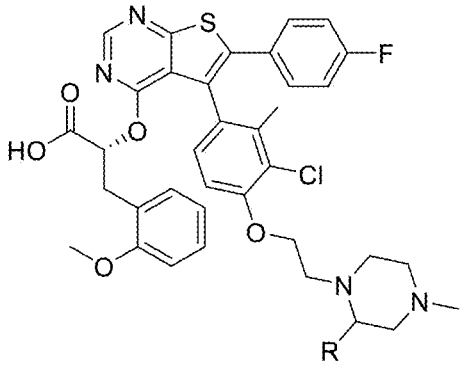
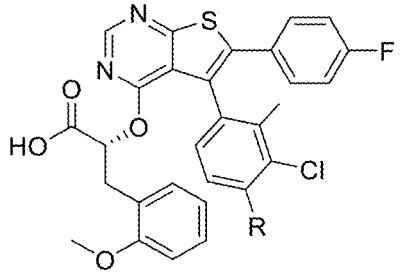
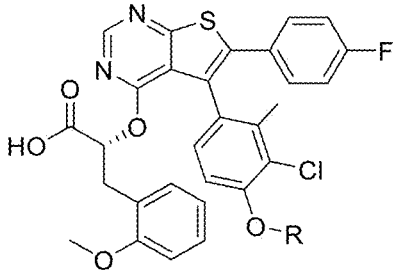
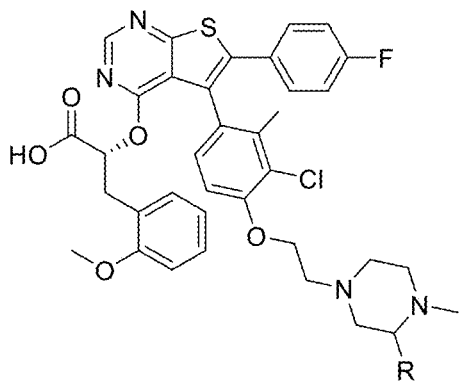
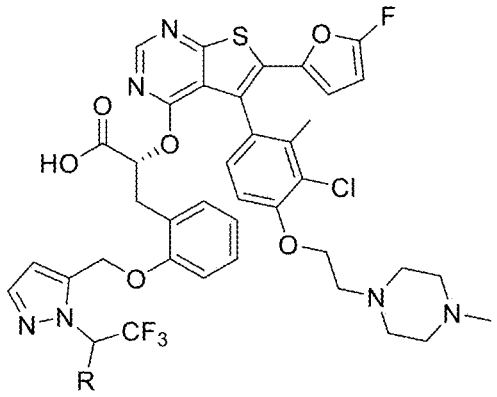
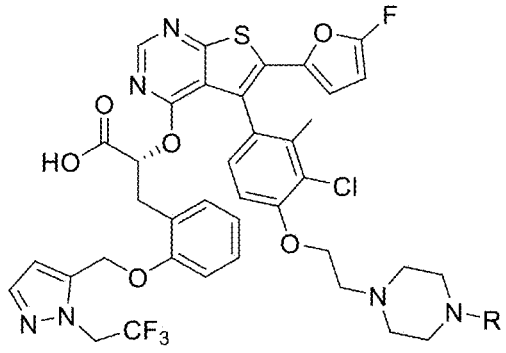
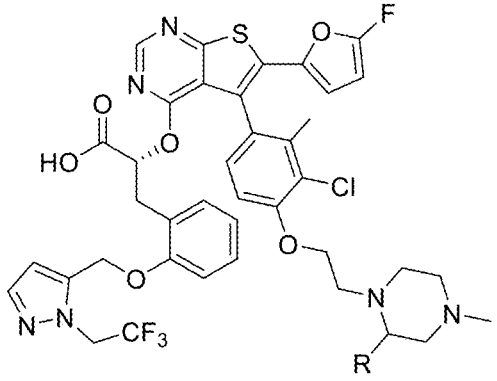









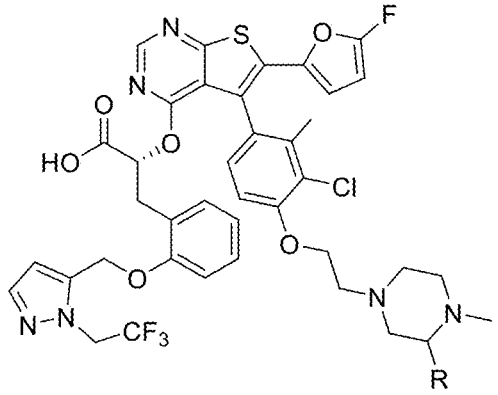
FIG. 3GG











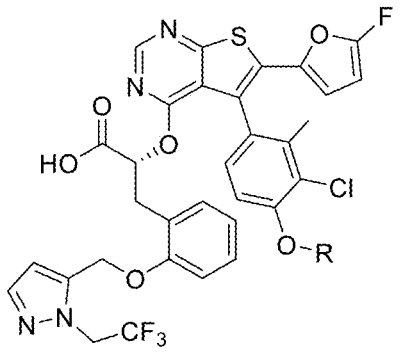


FIG. 3HH

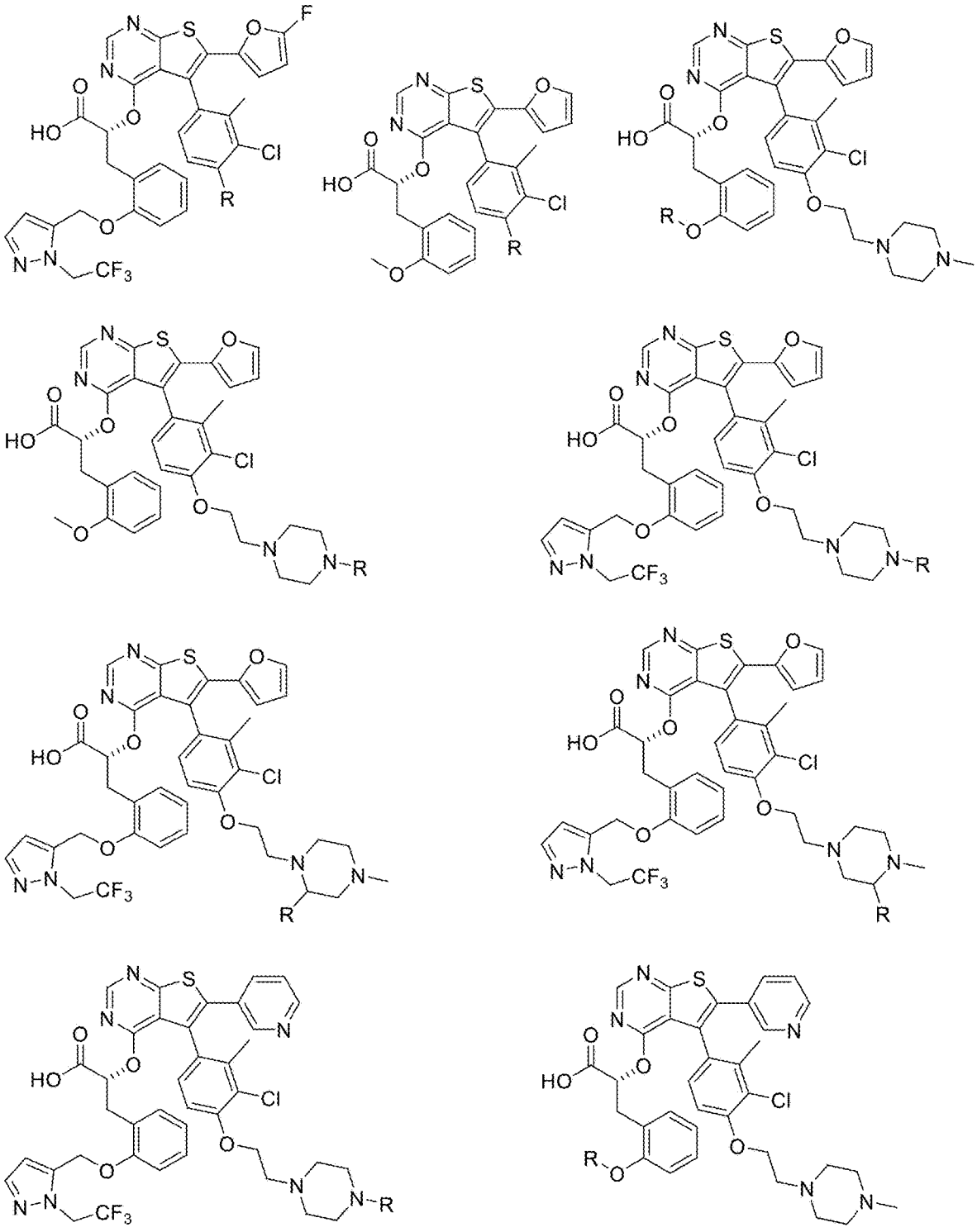
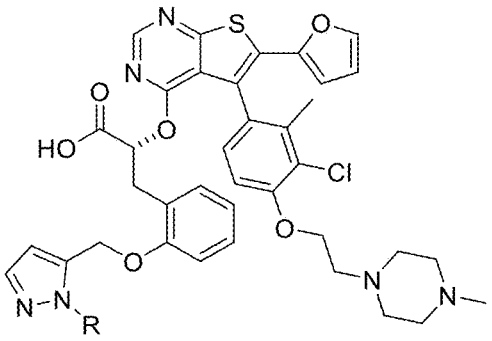
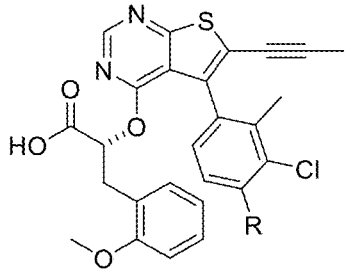
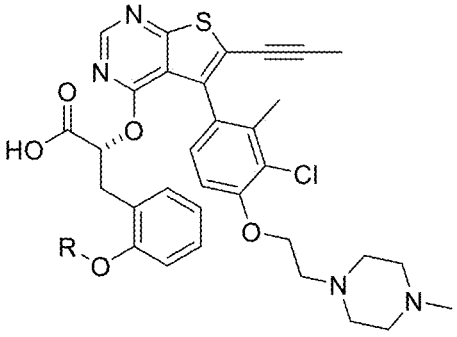
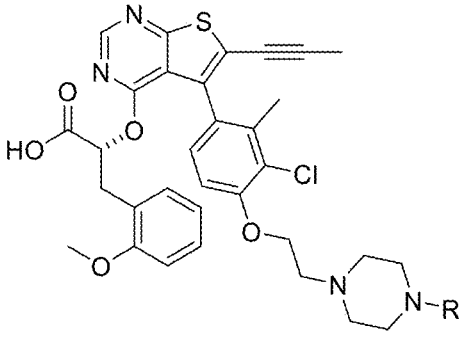


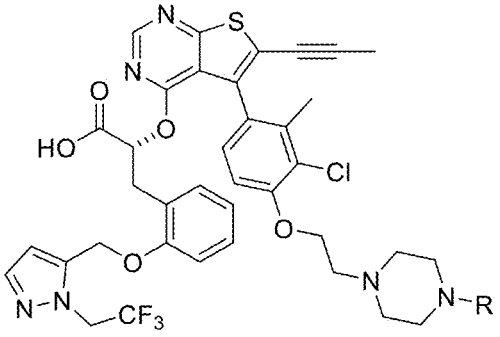
FIG. 3II

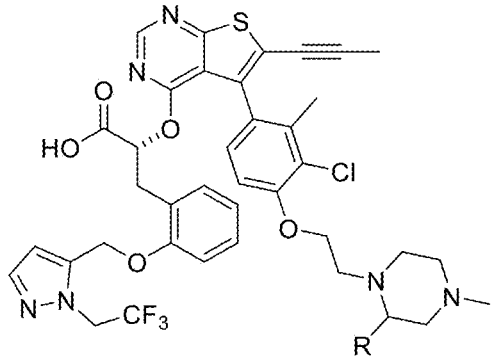


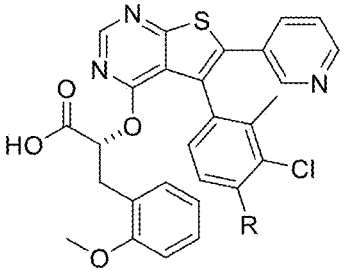












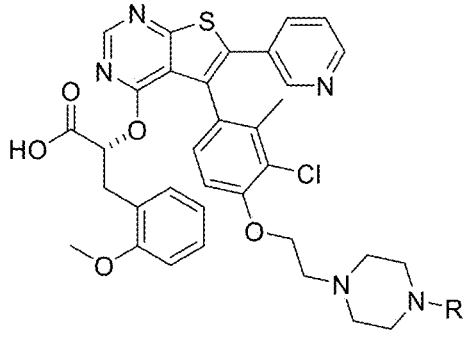
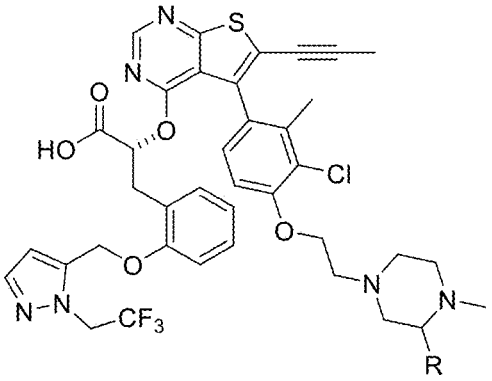
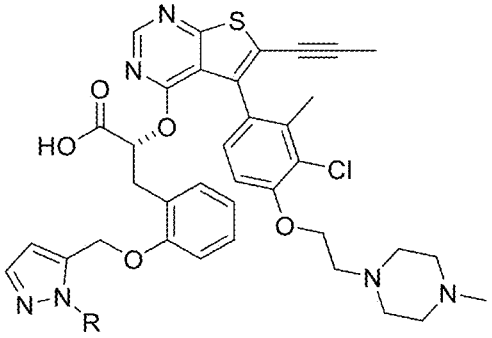
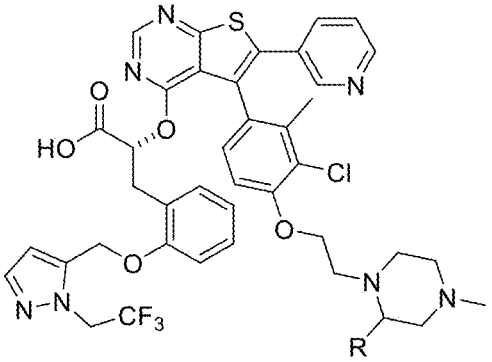
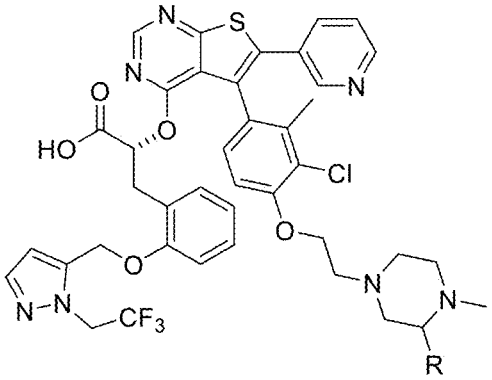


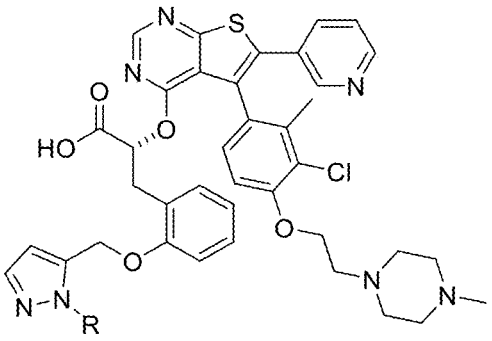
FIG. 3JJ

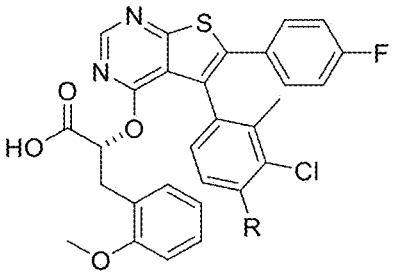


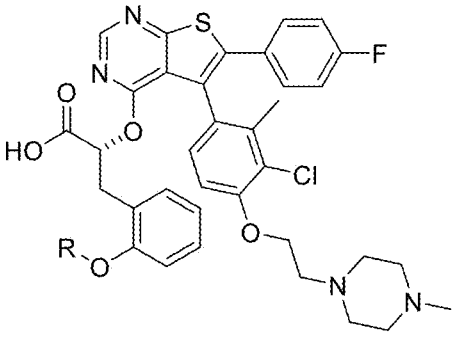












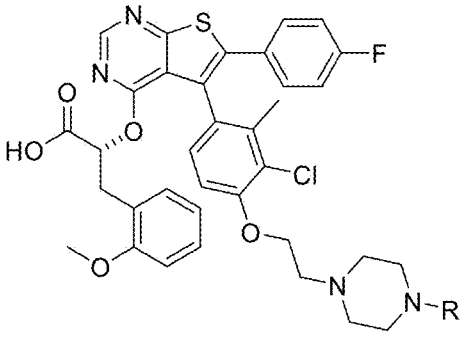


FIG. 3KK

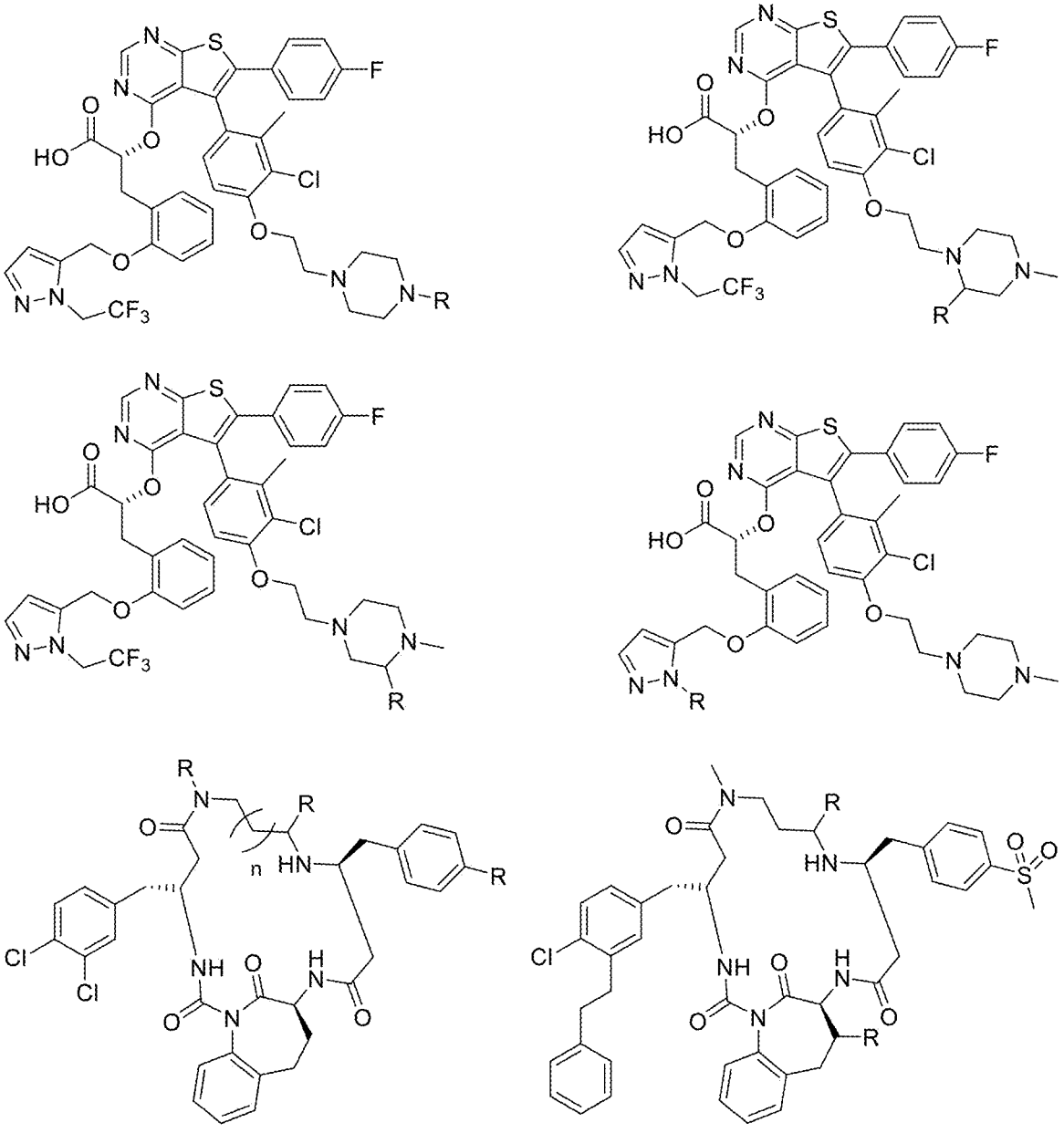


FIG. 3LL

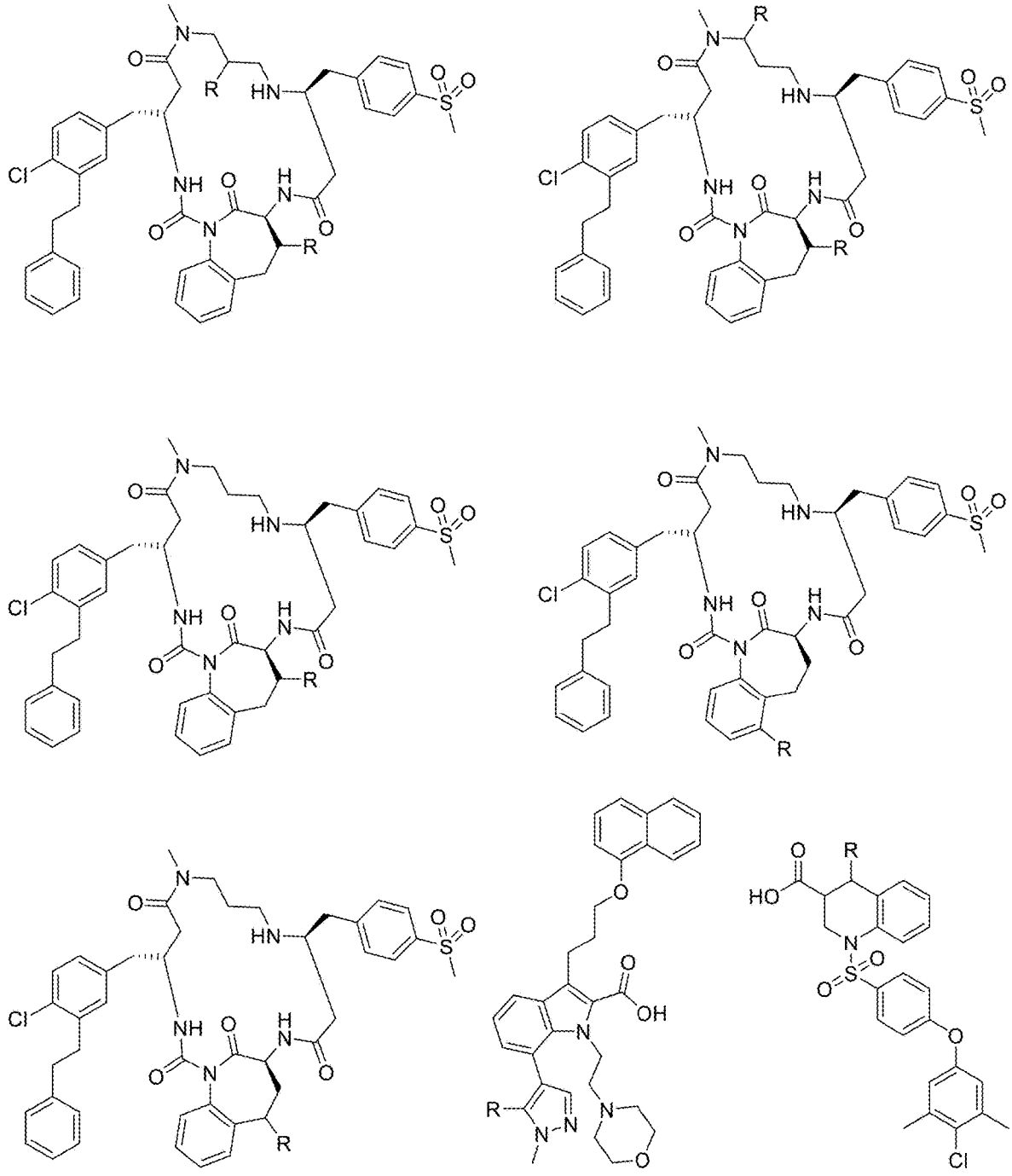


FIG. 3MM

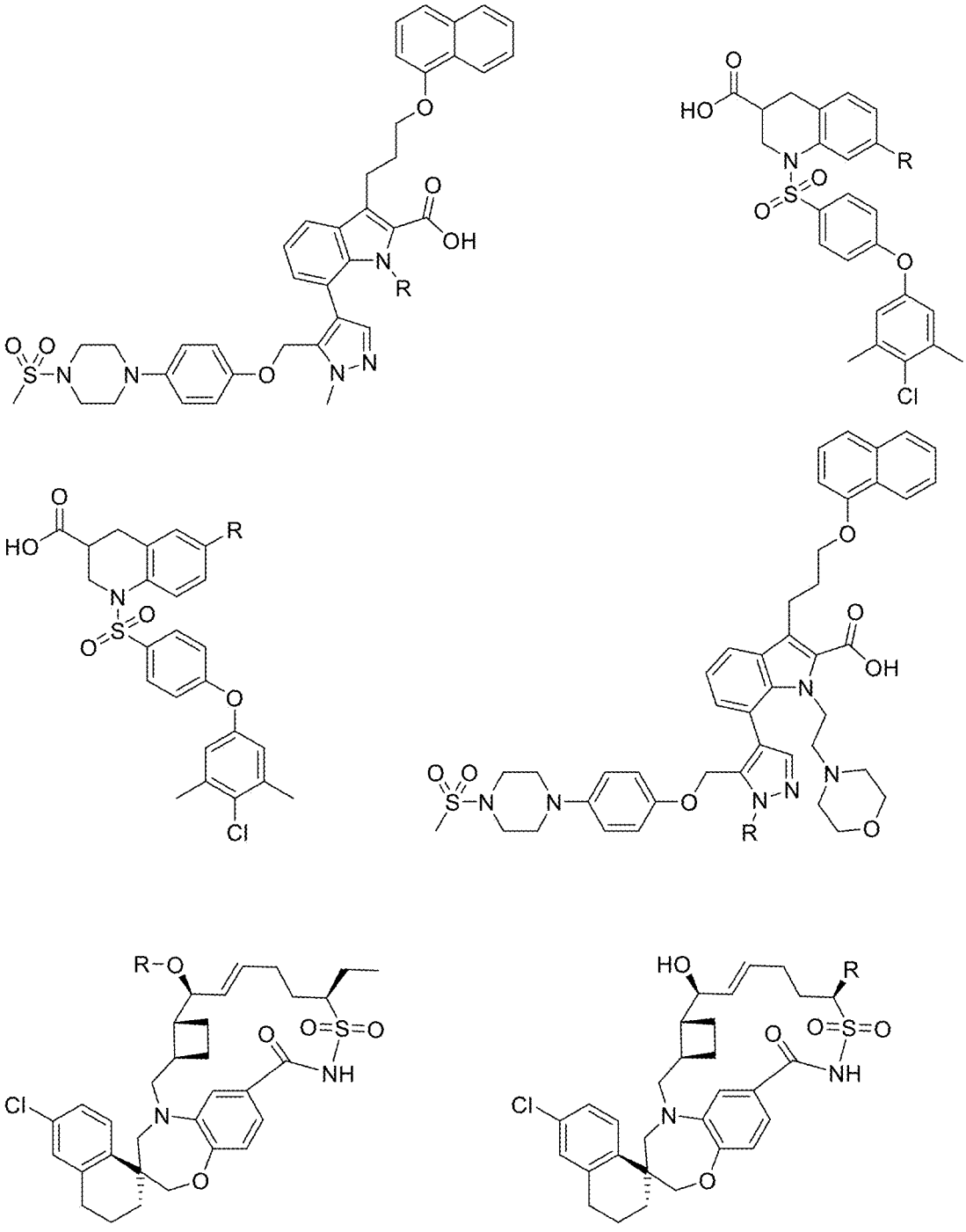


FIG. 3NN

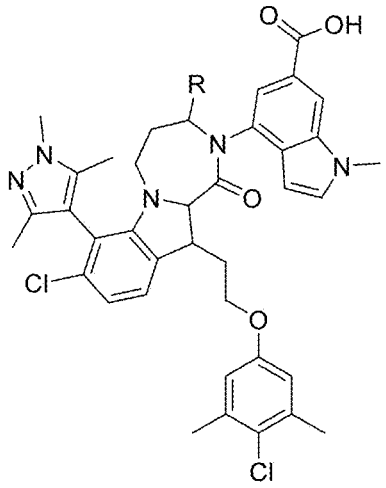
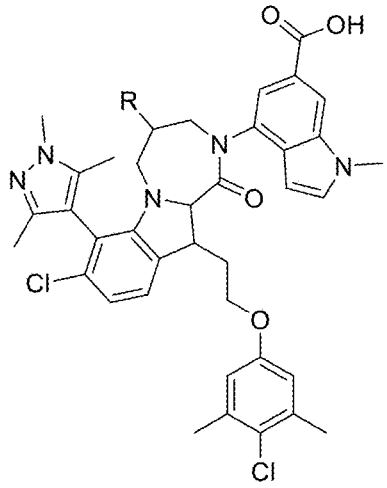
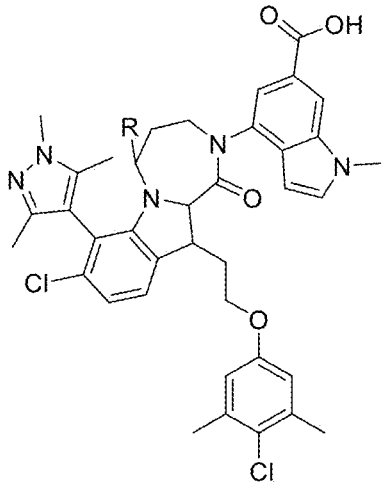
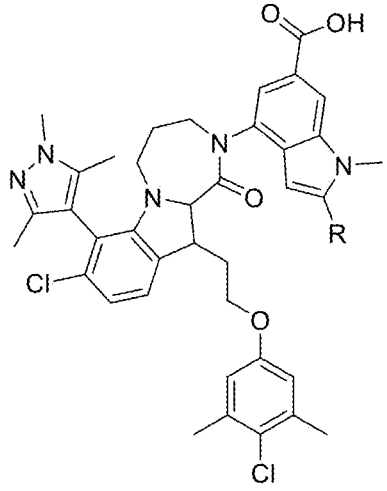
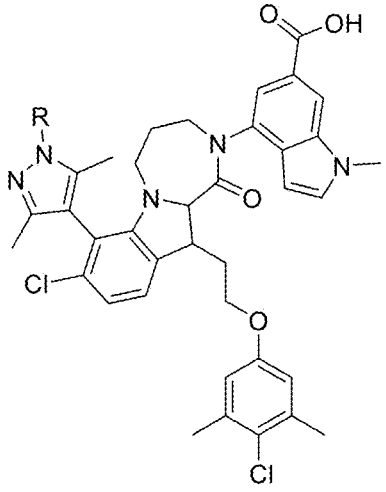
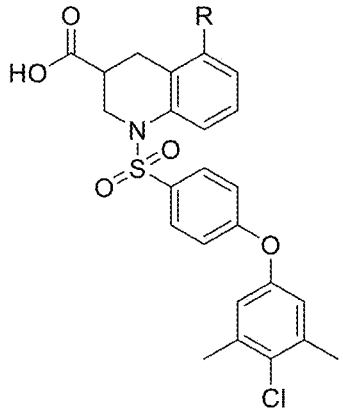







FIG. 3OO

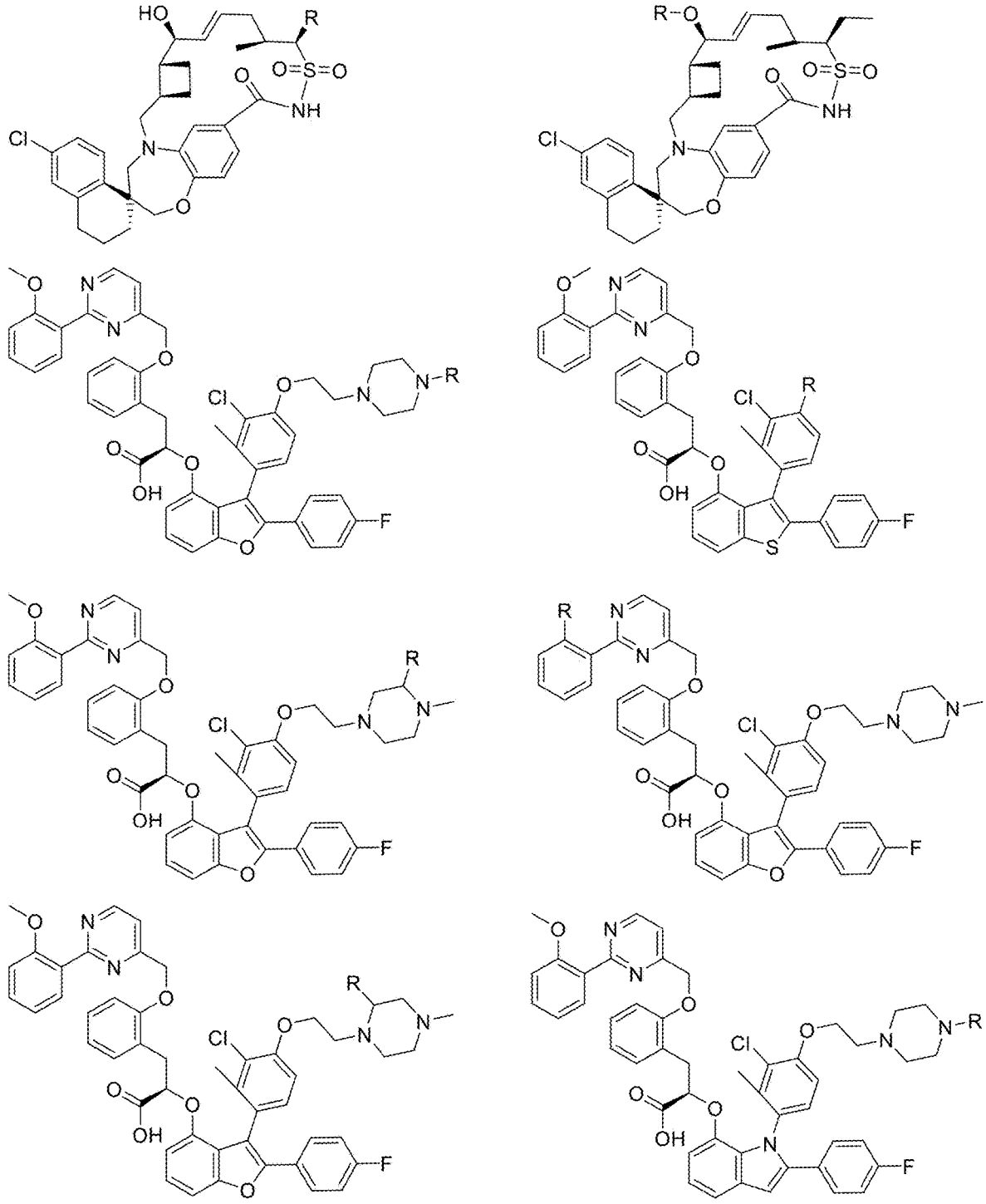


FIG. 3PP

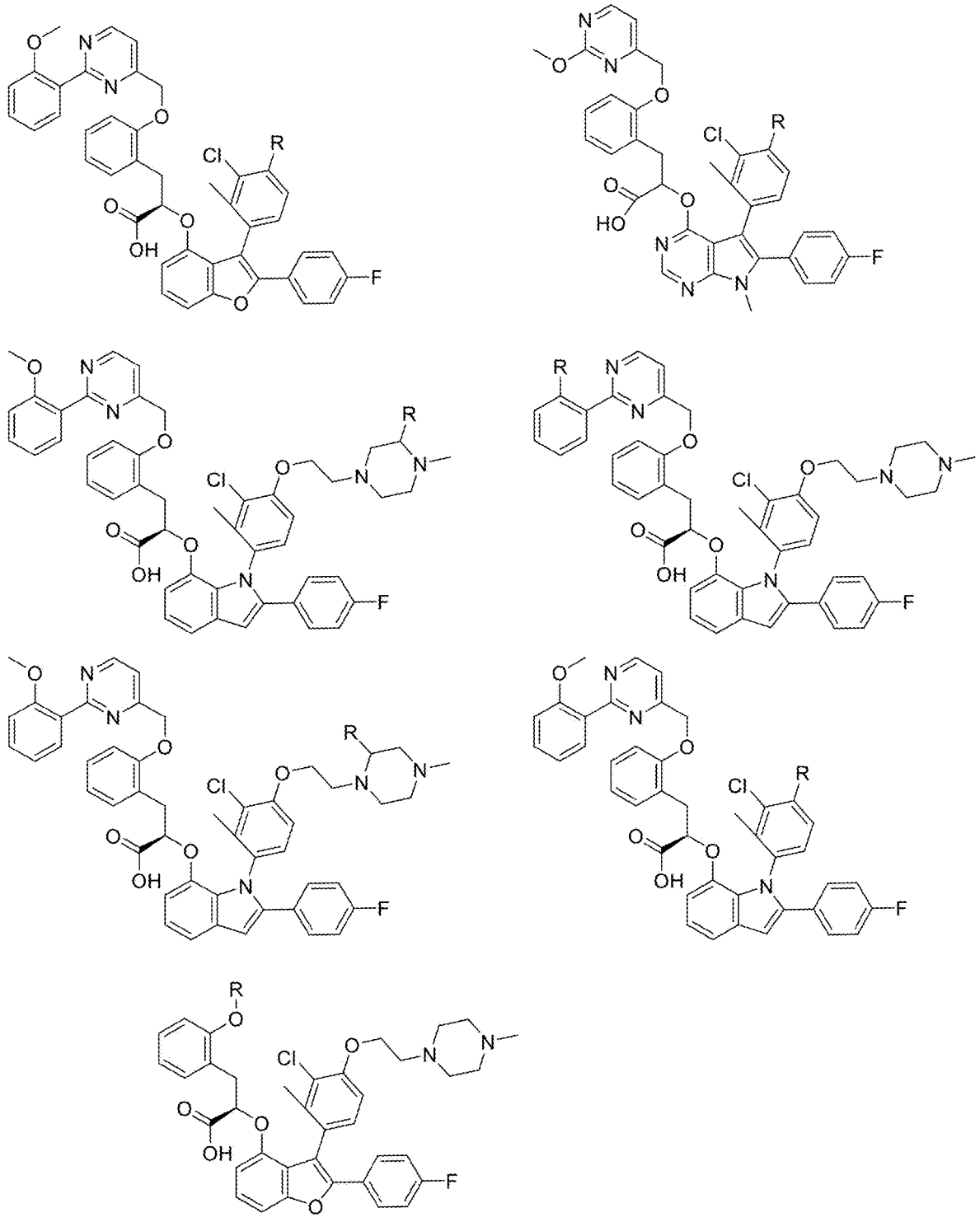


FIG. 3QQ

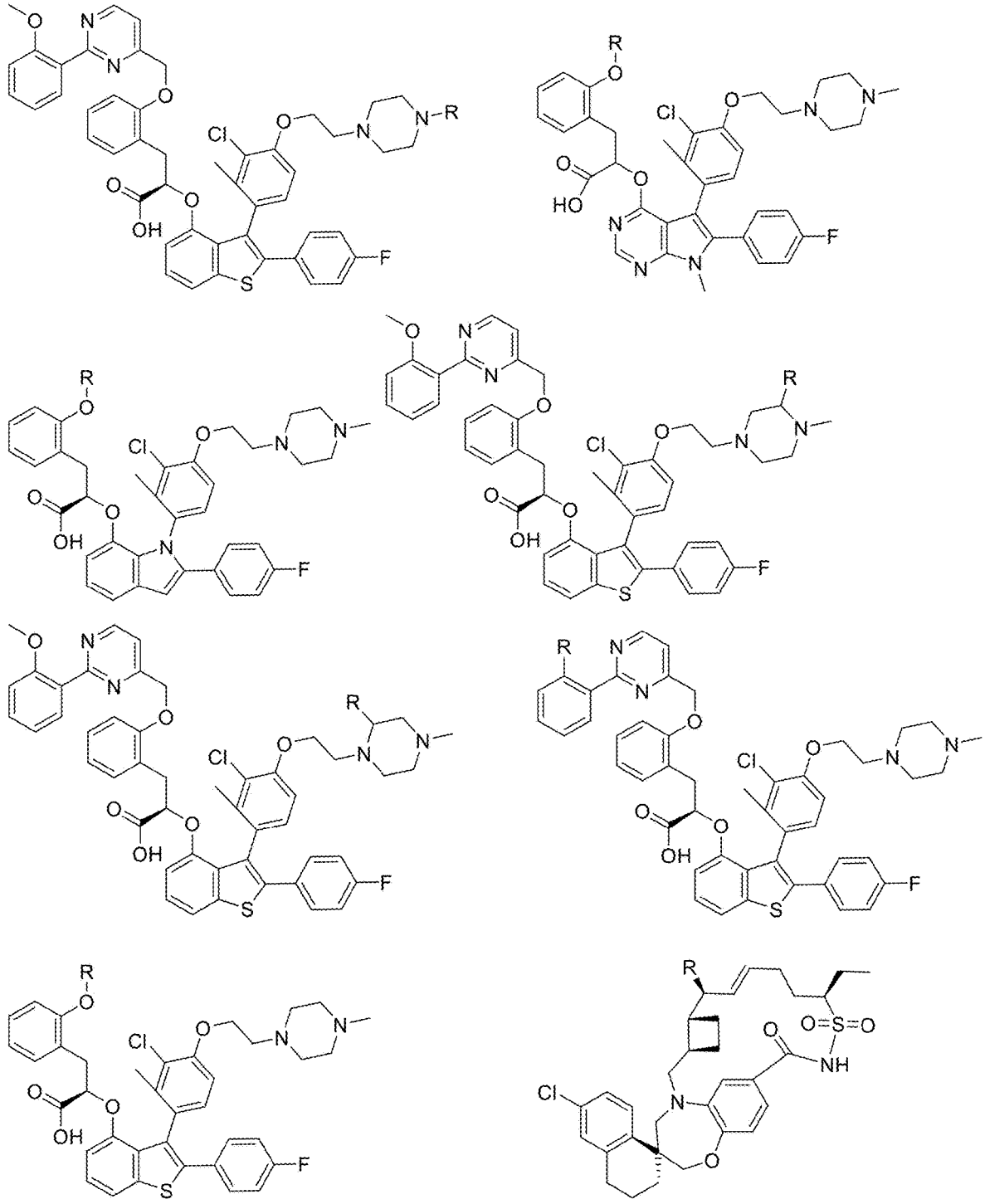


FIG. 3RR

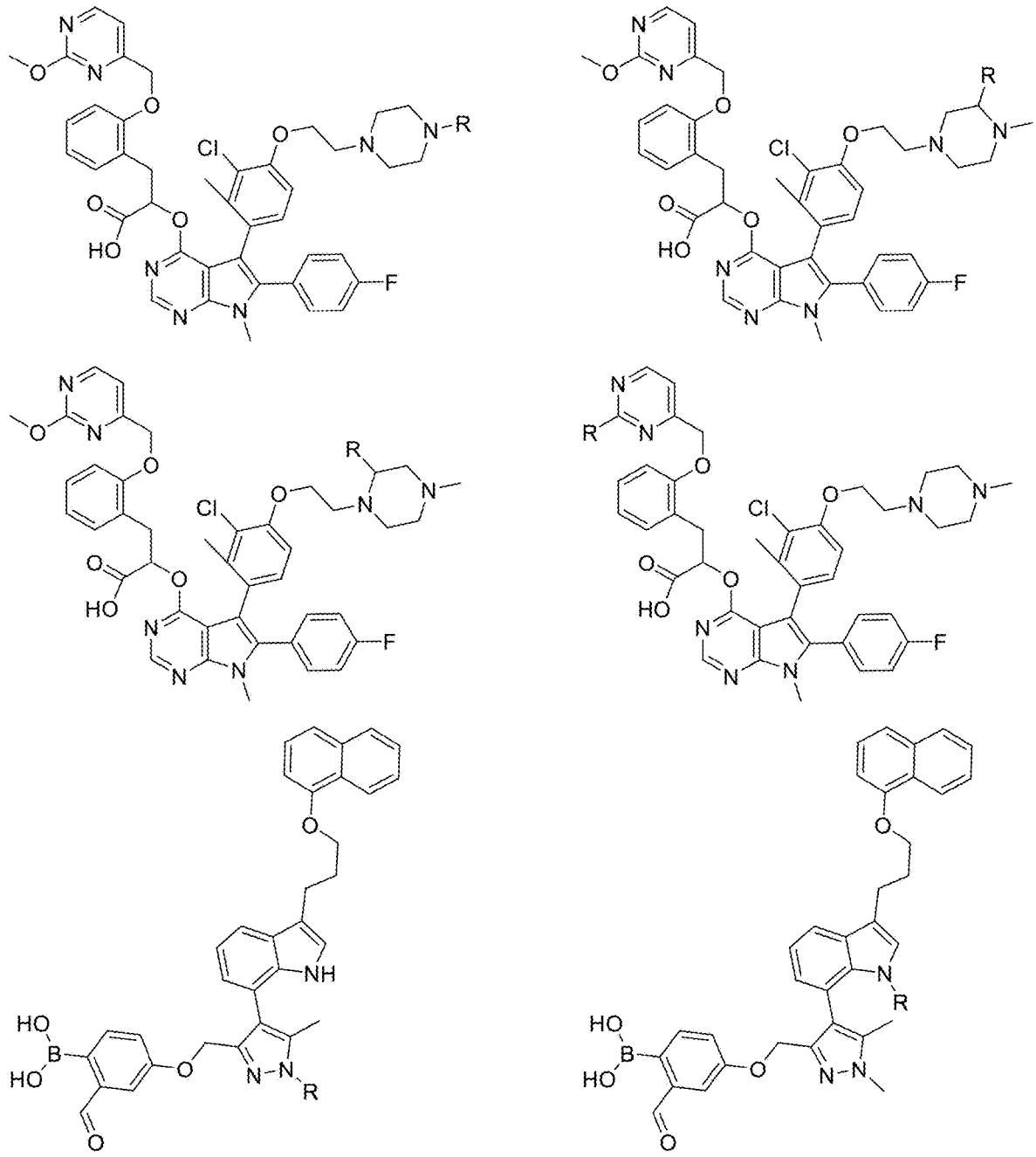


FIG. 3SS

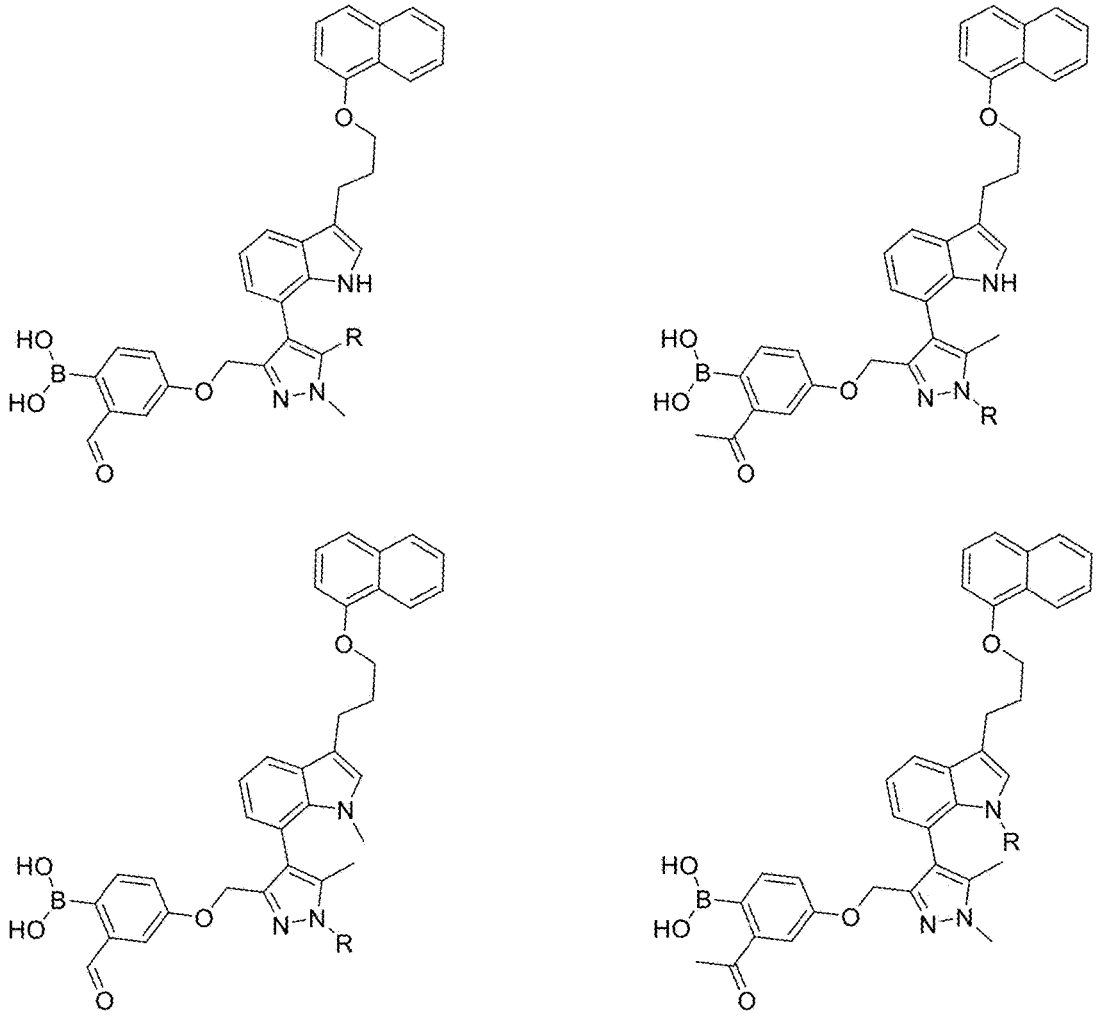


FIG. 3TT

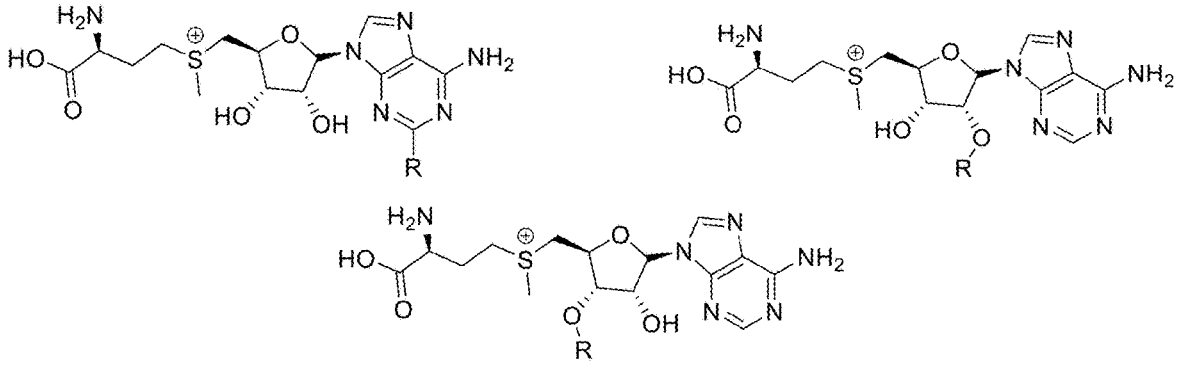


FIG. 3UU

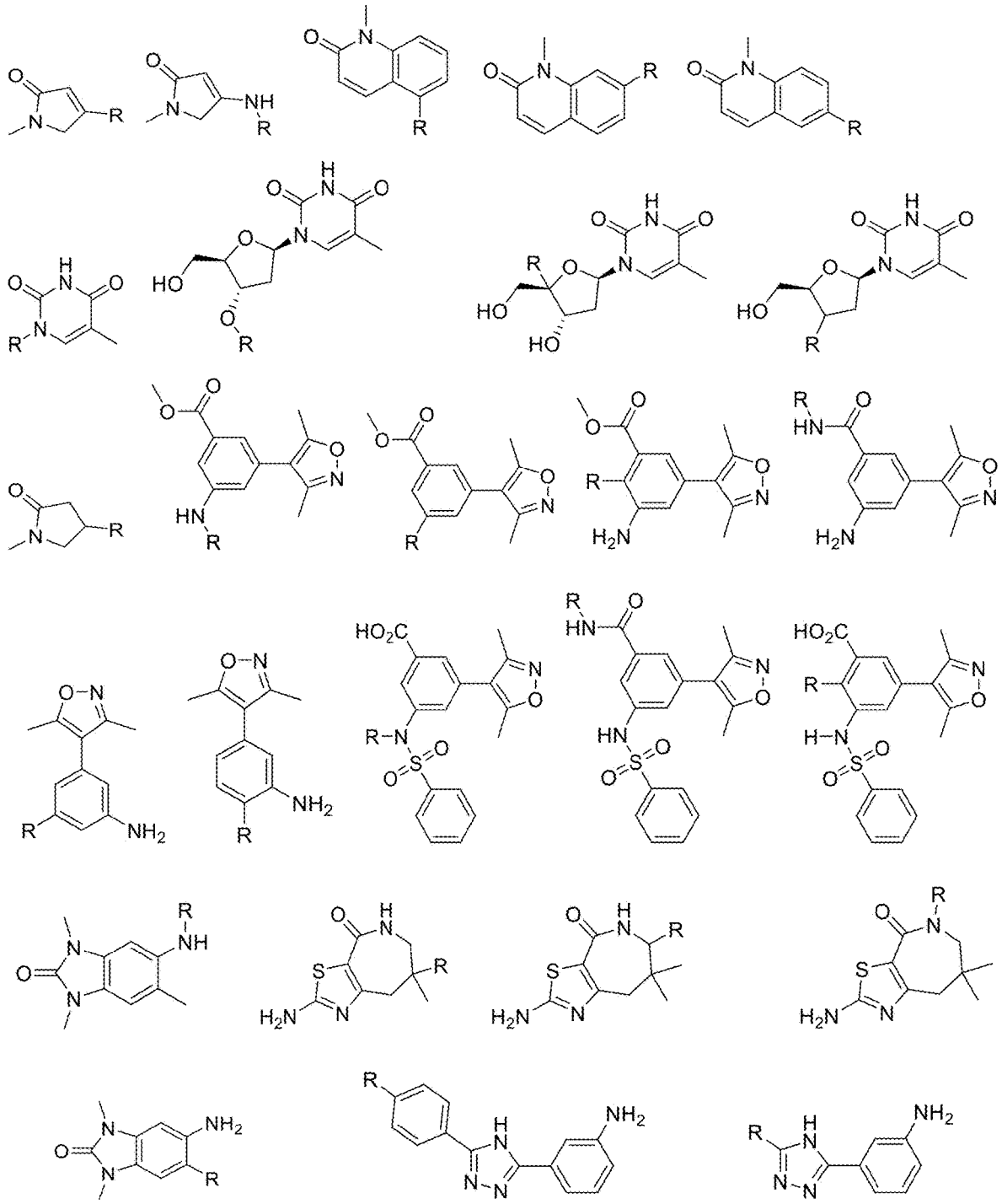


FIG. 3VV

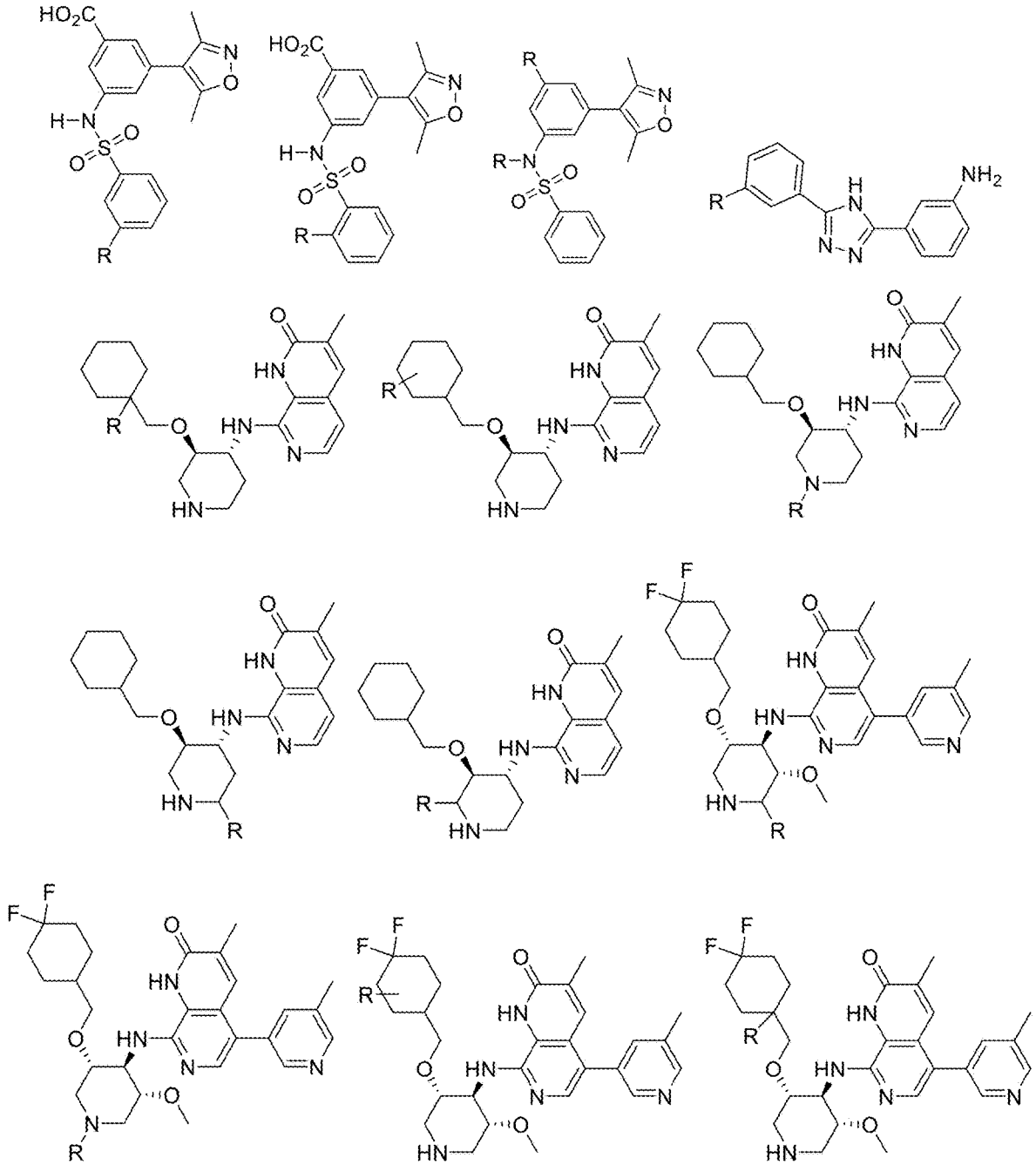


FIG. 3WW

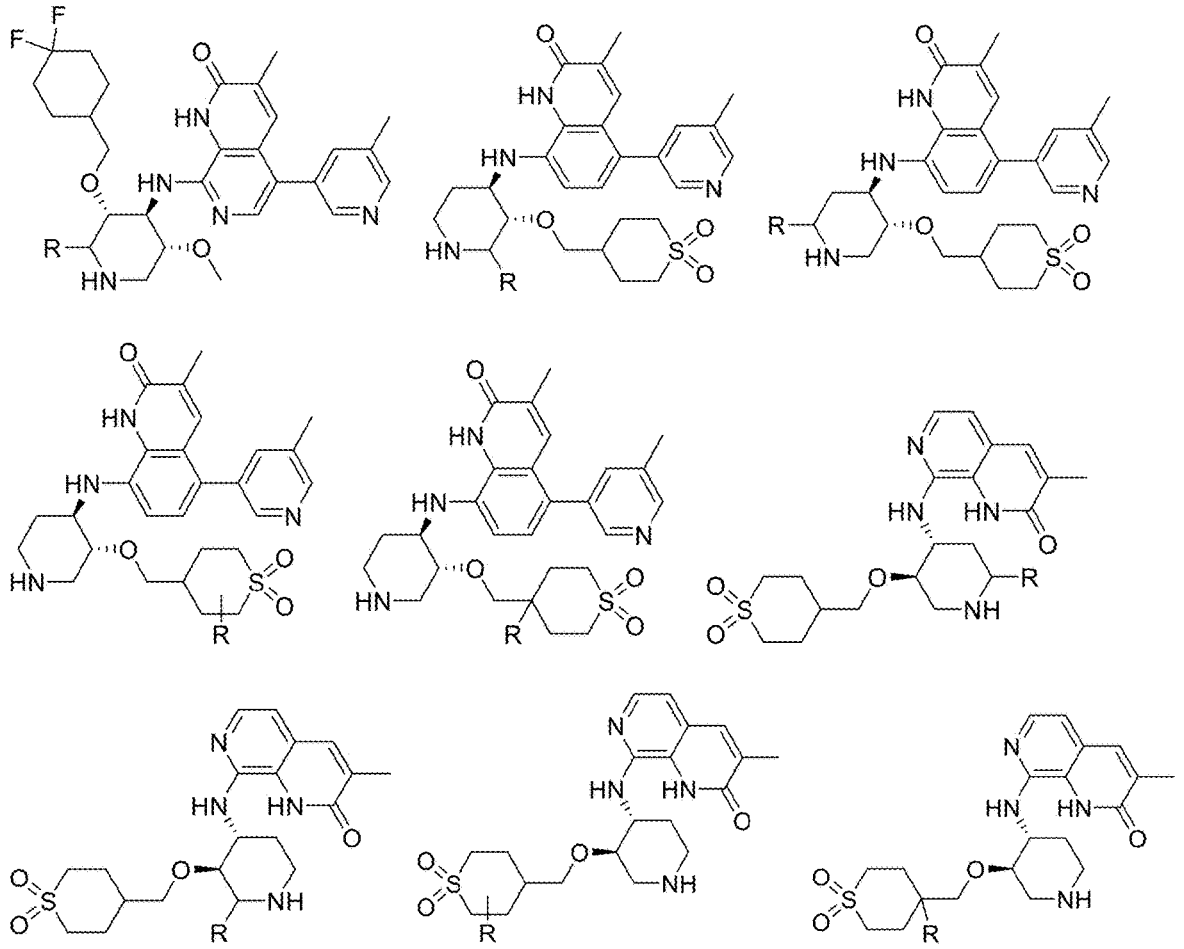


FIG. 3XX

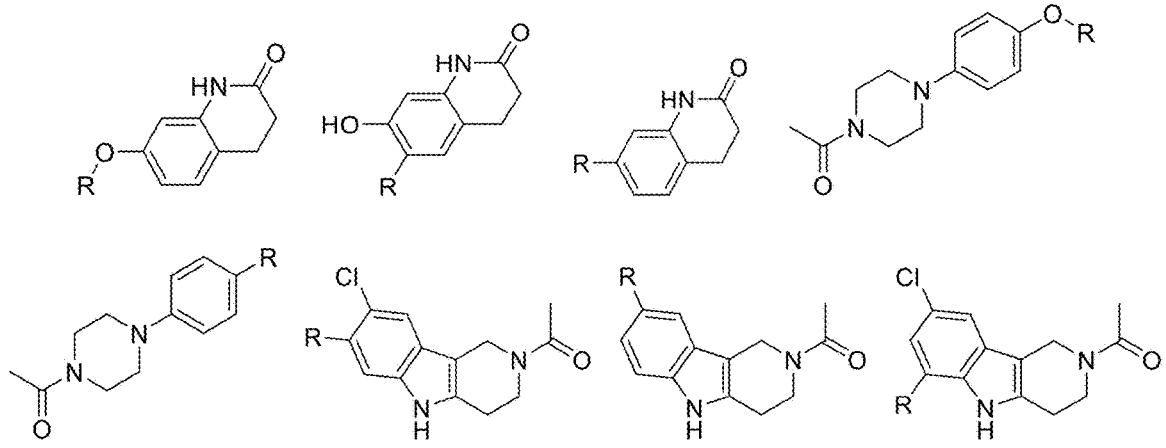


FIG. 3YY

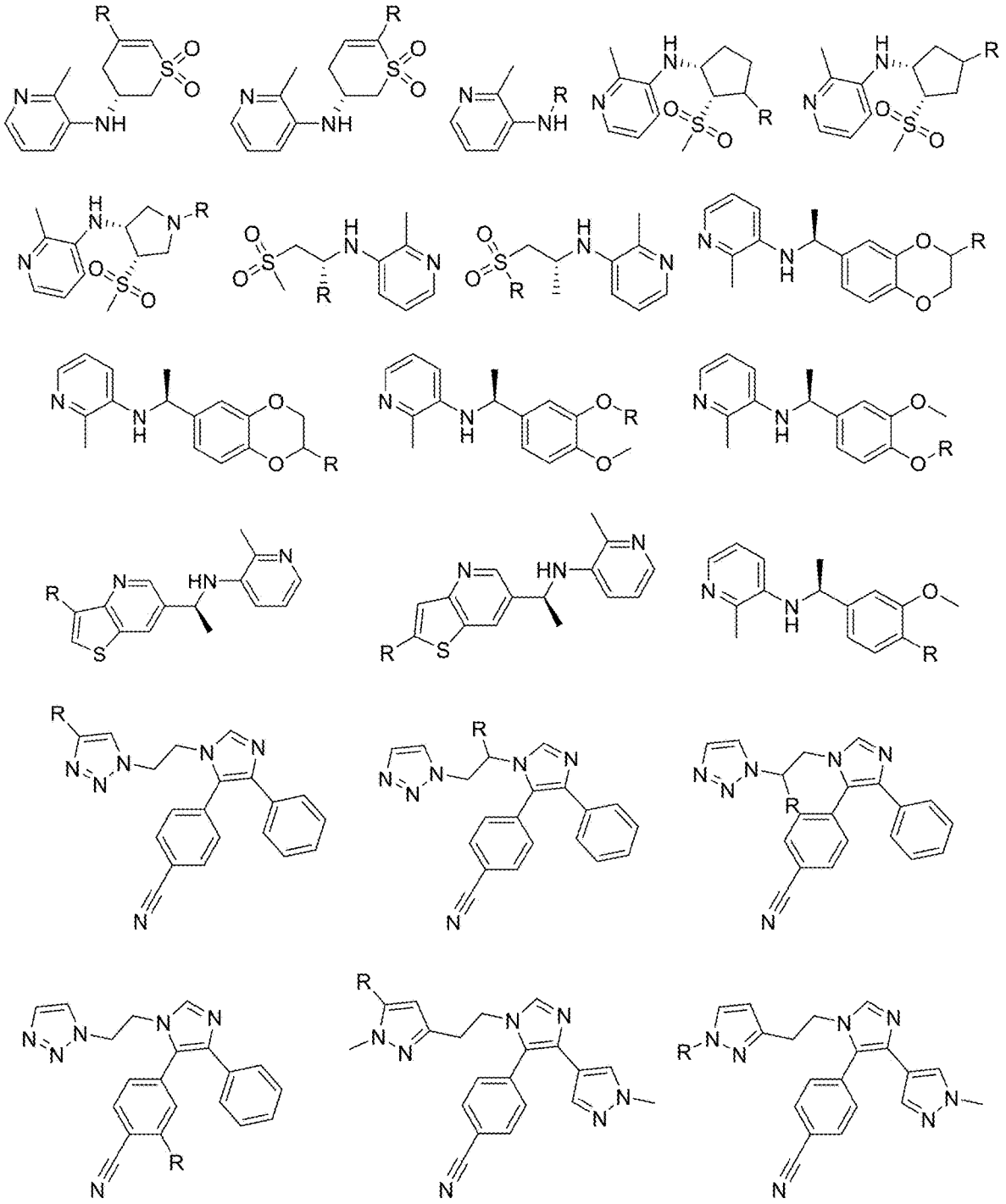
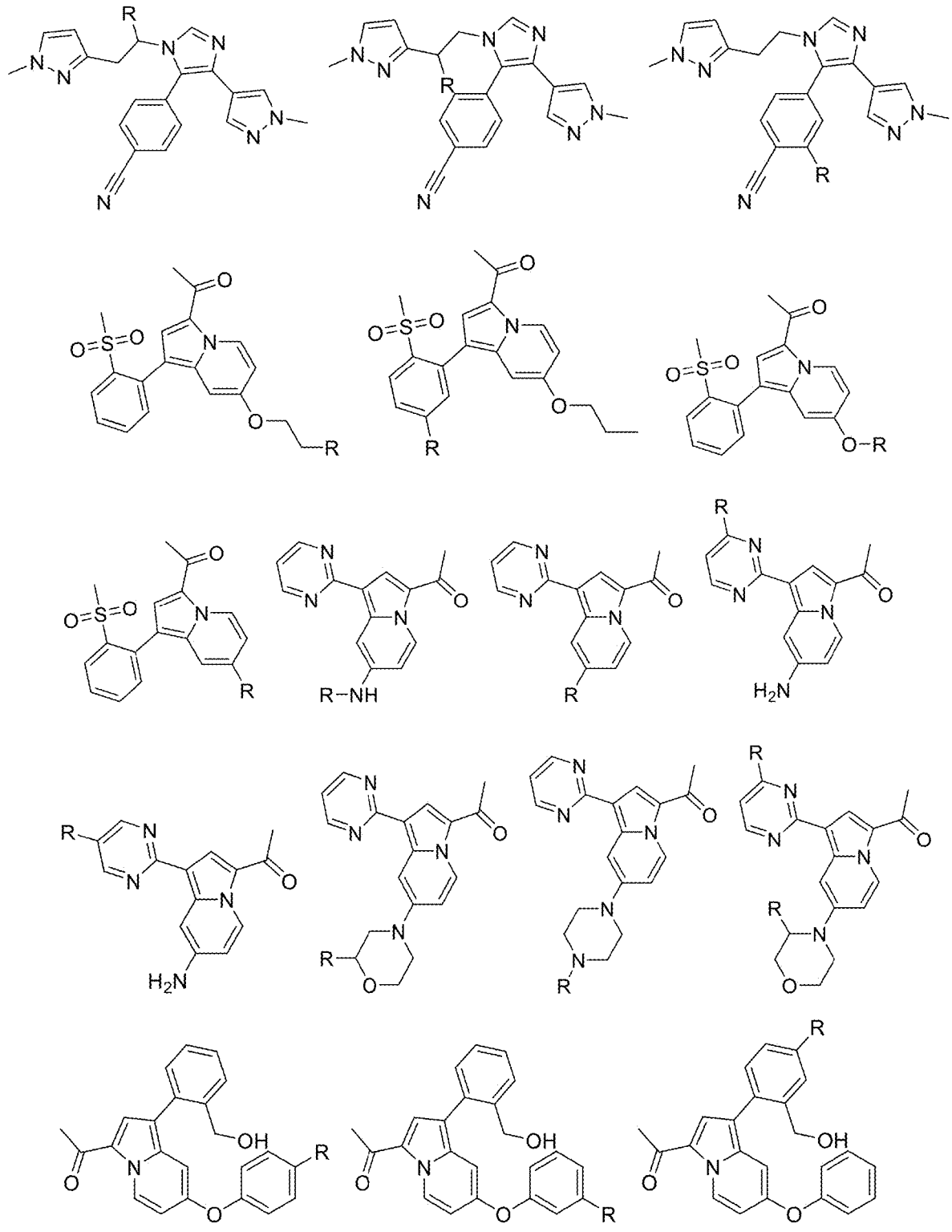


FIG. 3ZZ



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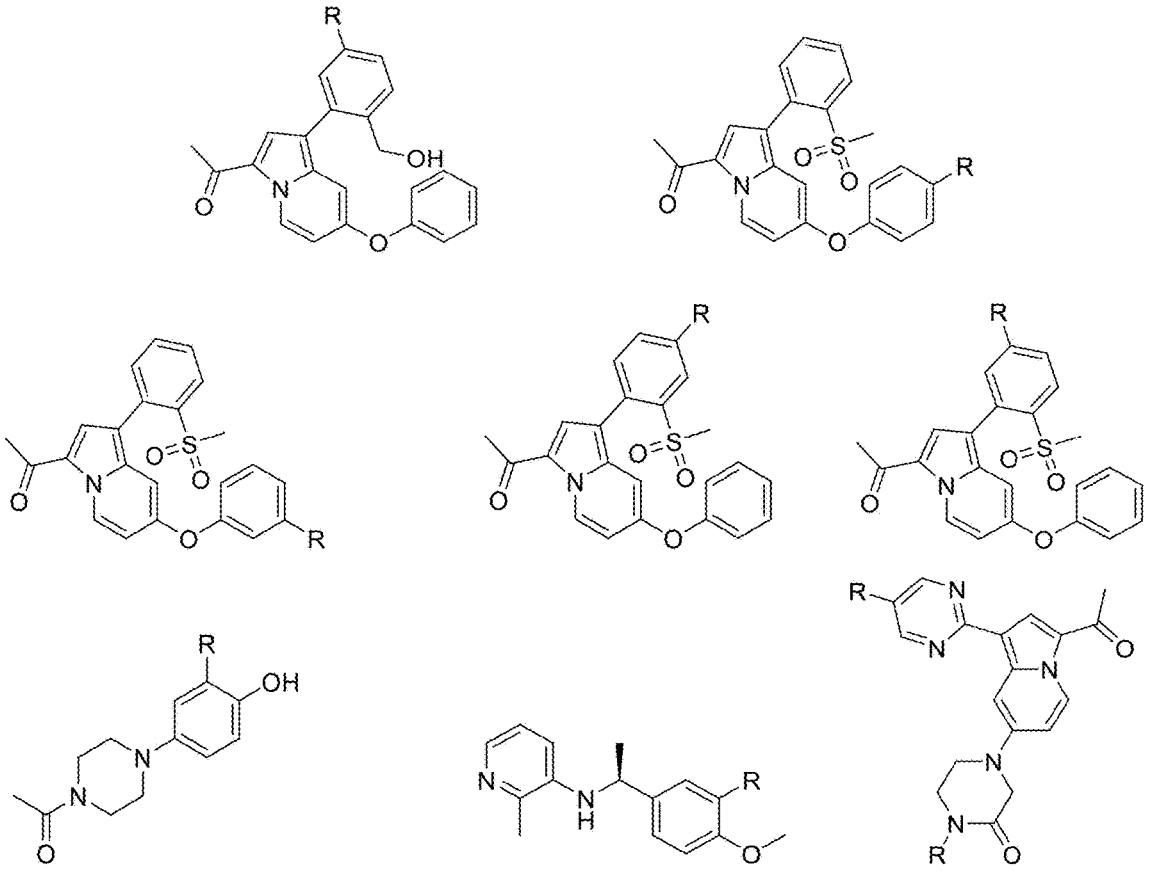


FIG. 3BBB

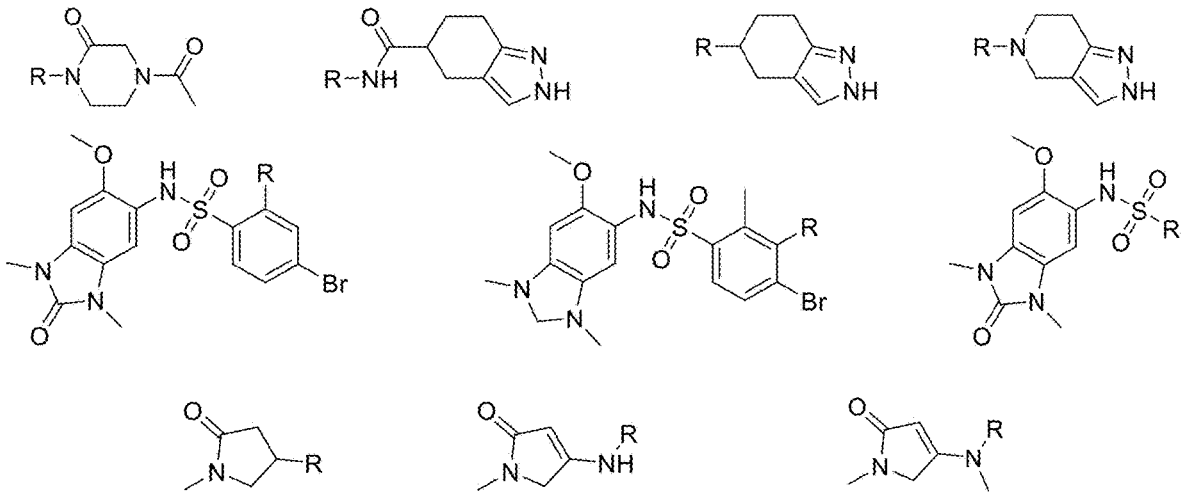


FIG. 3CCC

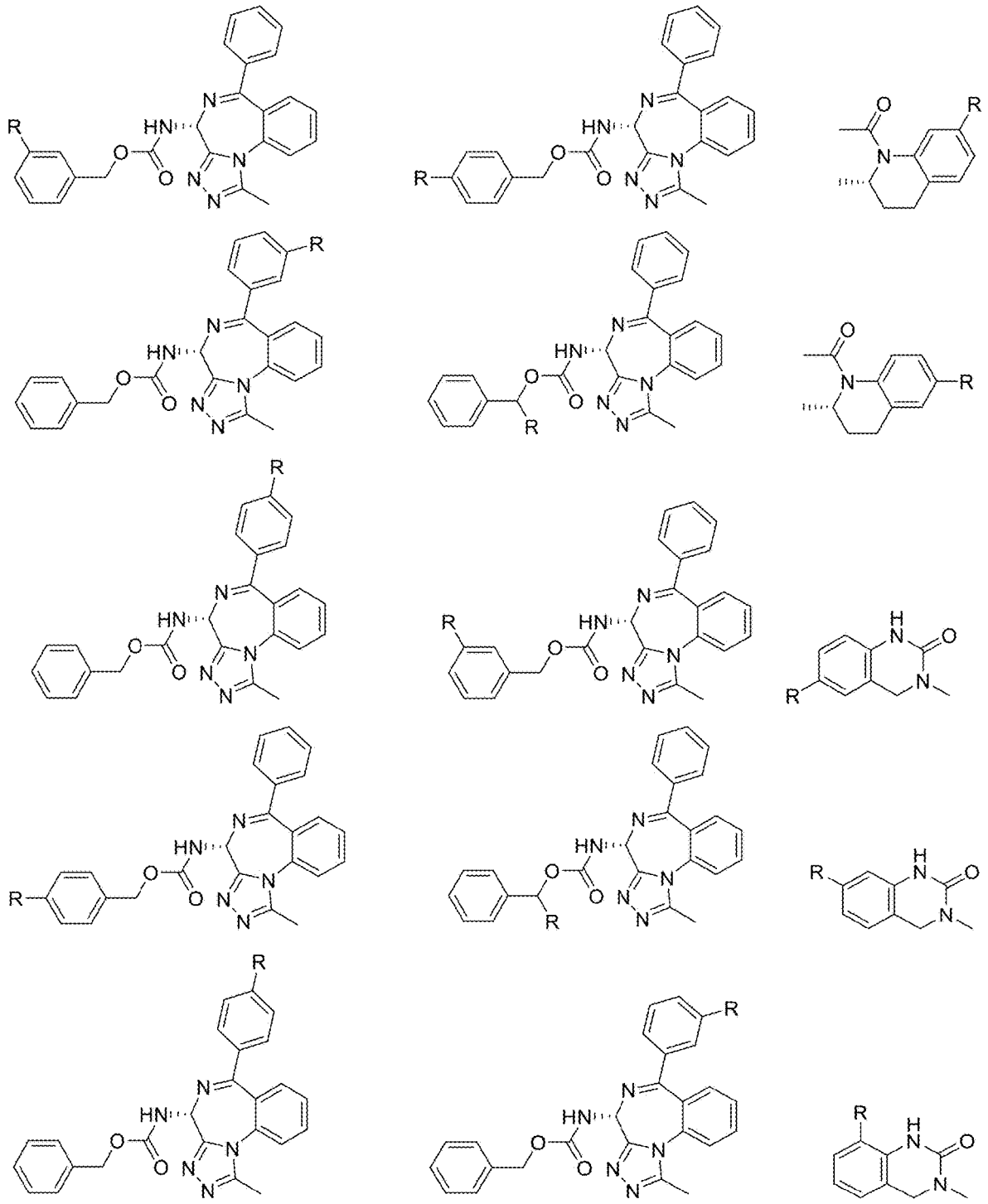


FIG. 3DDD

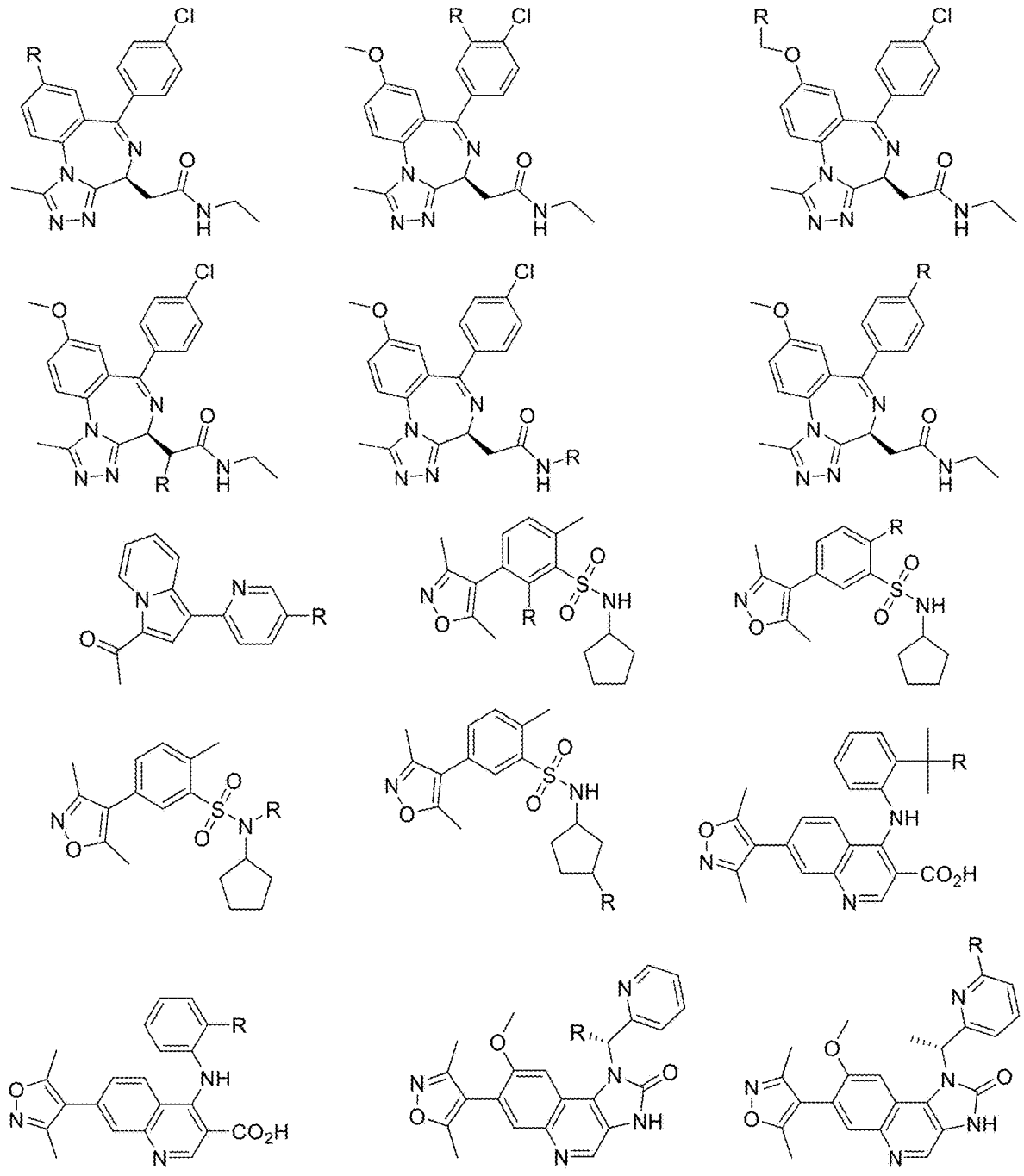


FIG. 3EEE

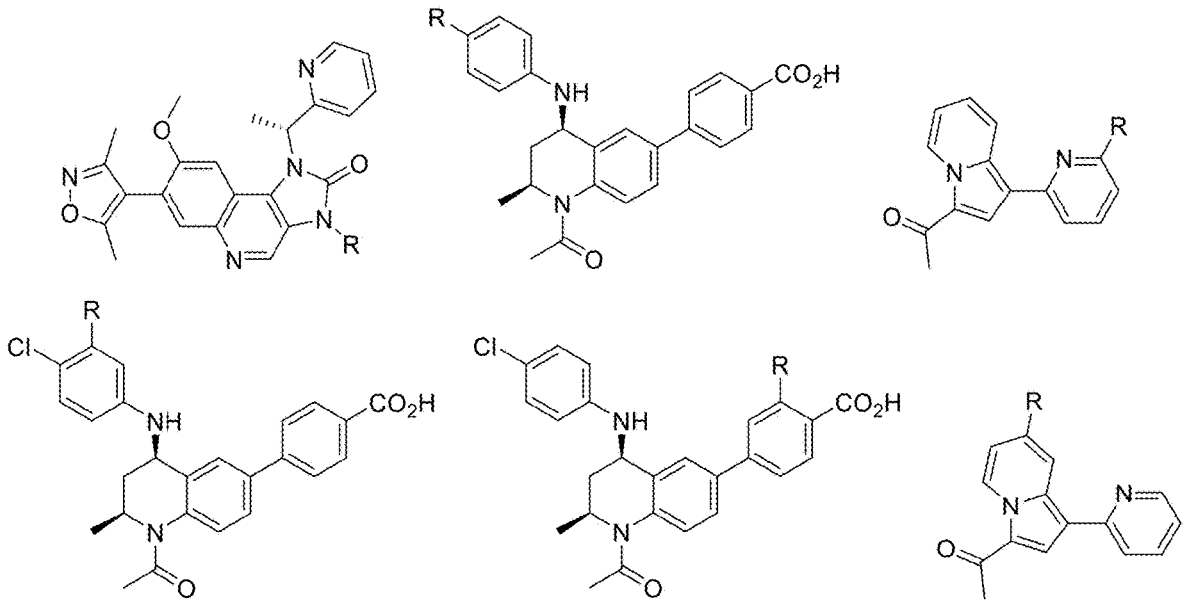


FIG. 3FFF

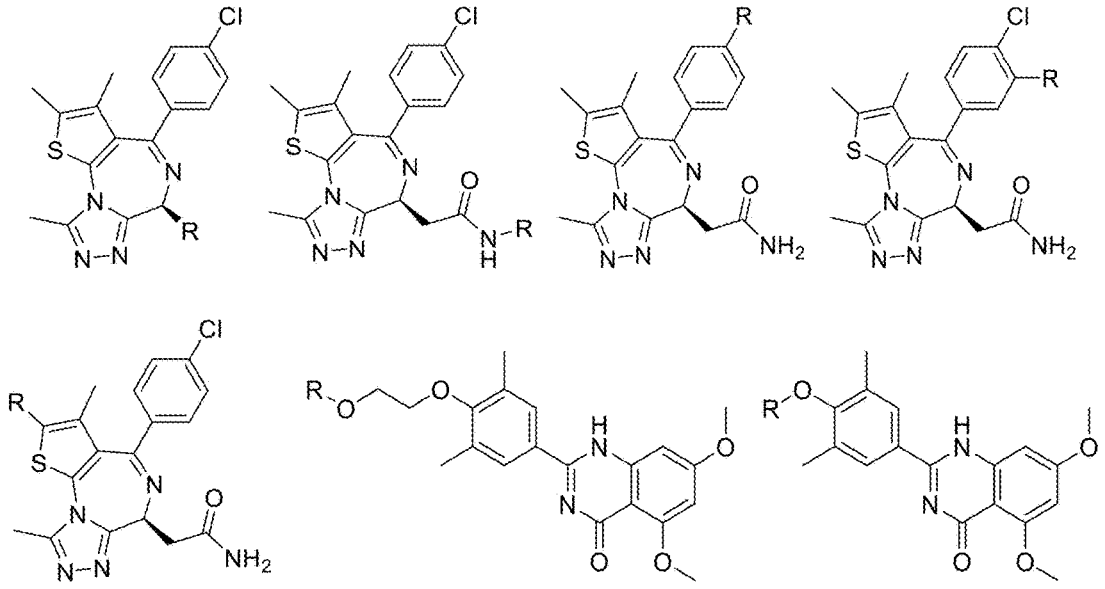


FIG. 3GGG

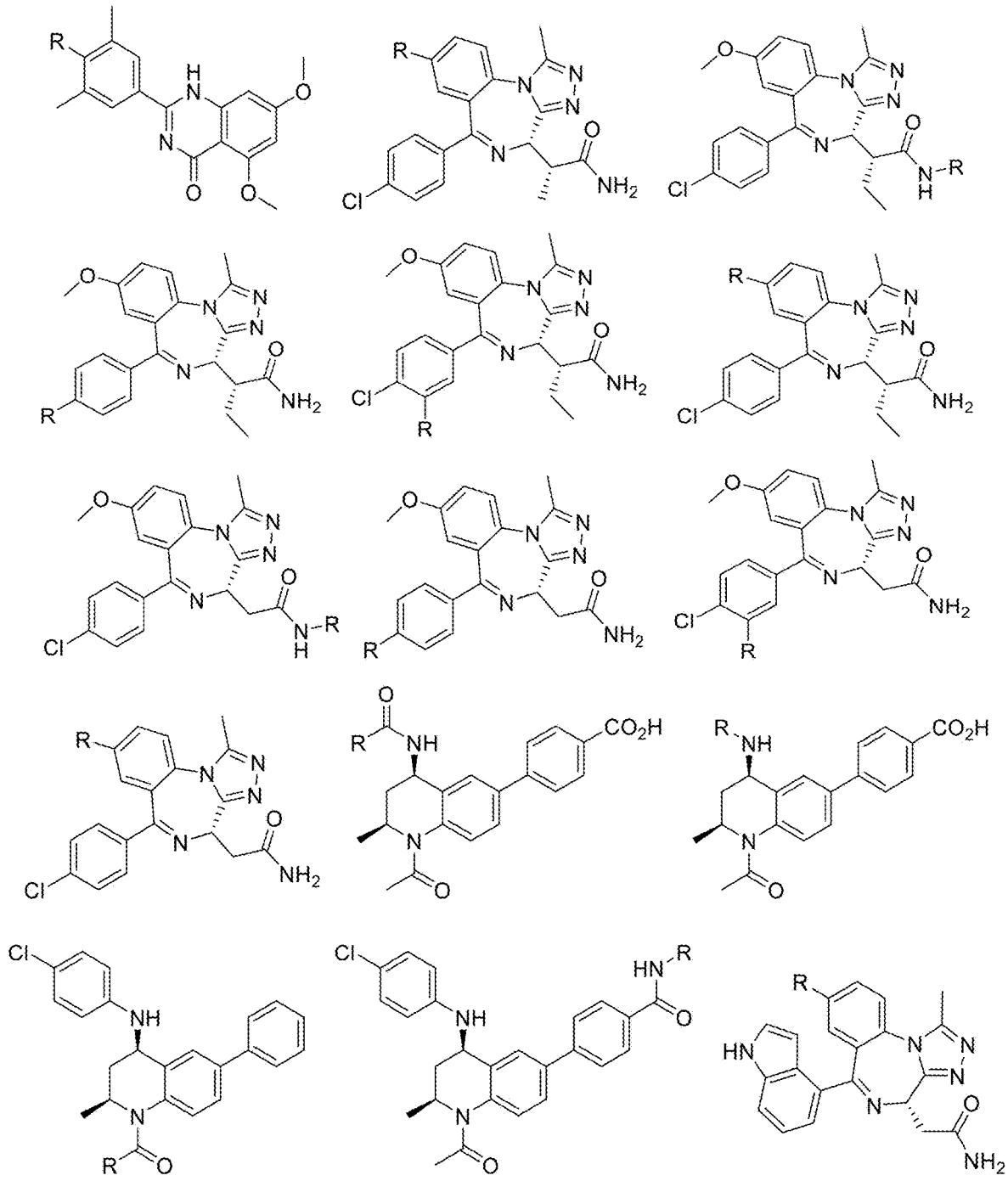


FIG. 3HHH

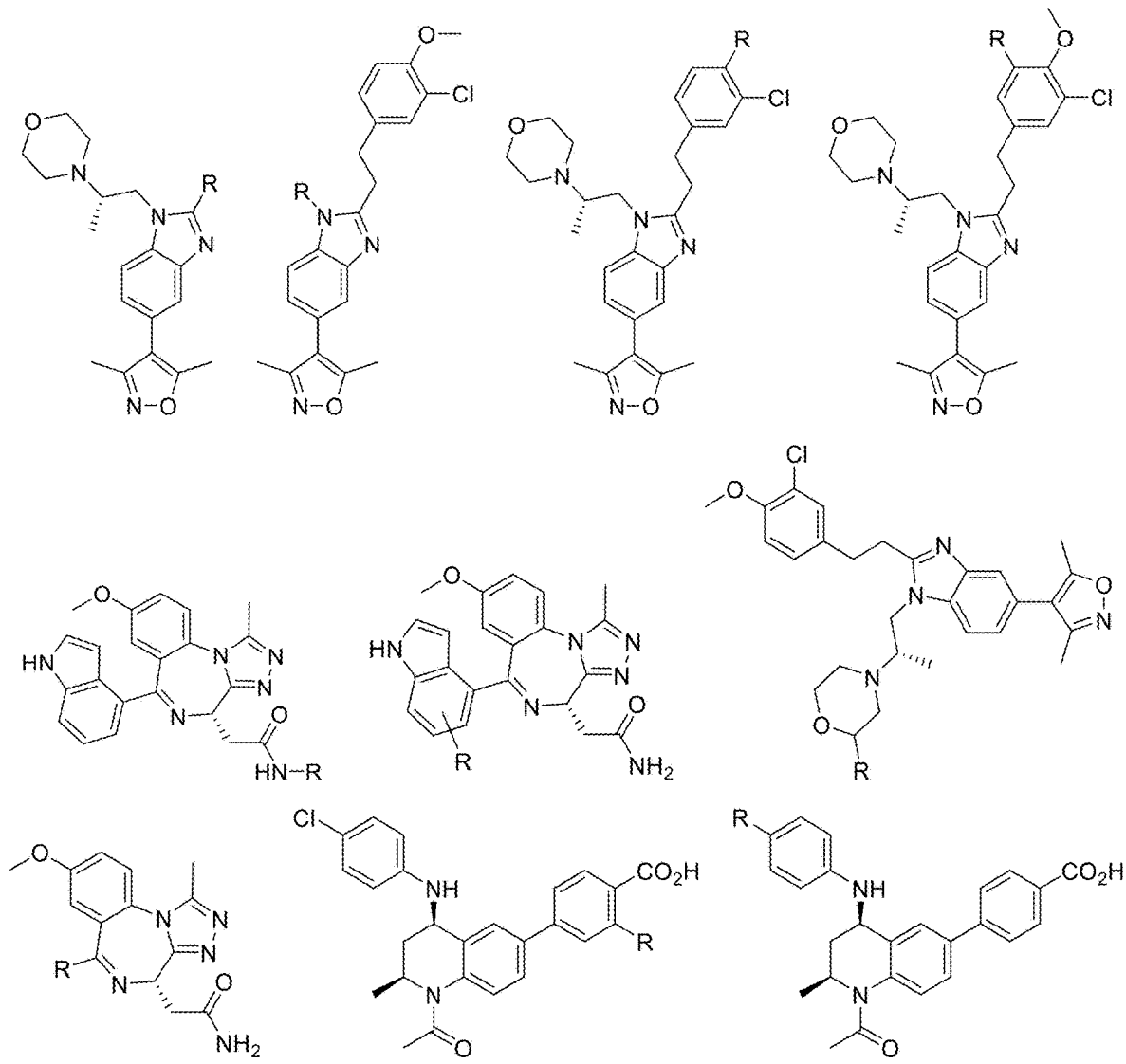


FIG. 3III

FIG. 3JJJ

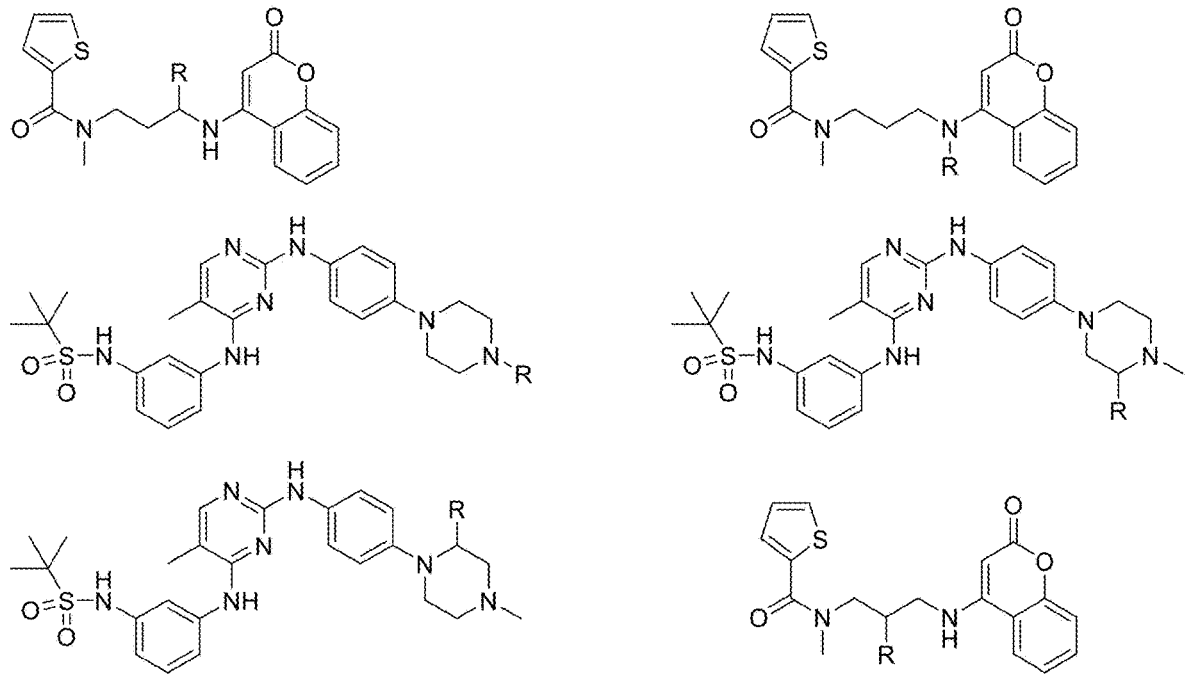


FIG. 3KKK

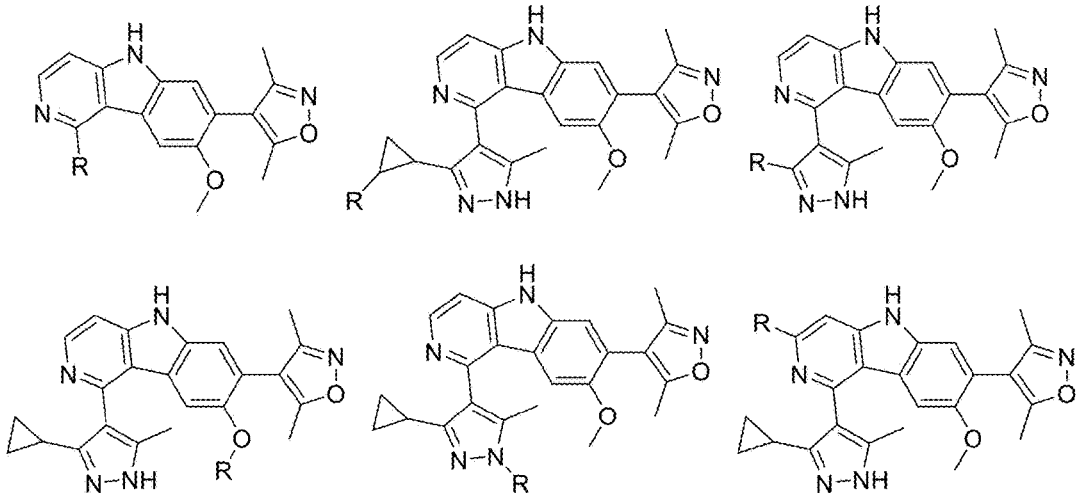


FIG. 3LLL

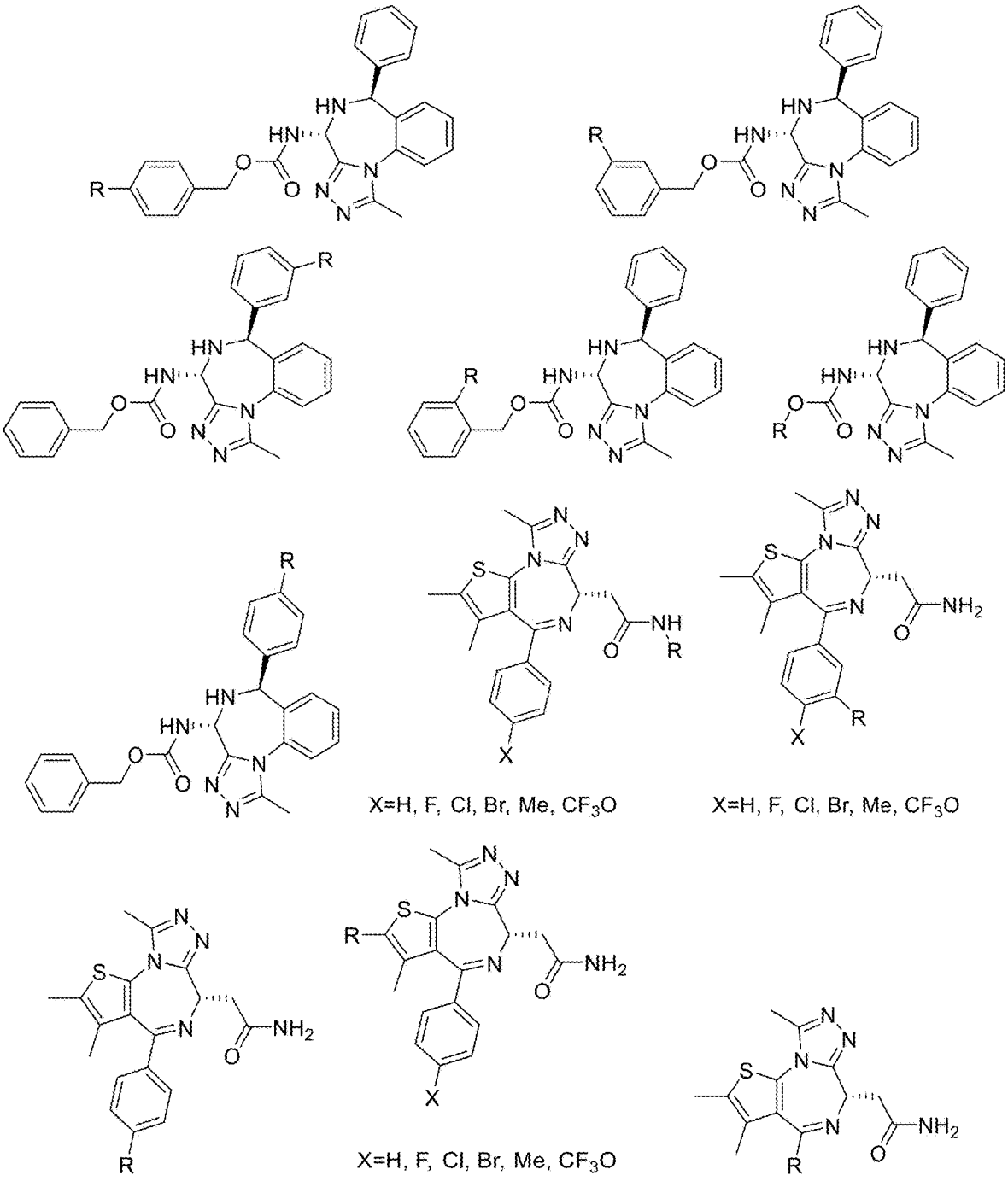


FIG. 3MMM

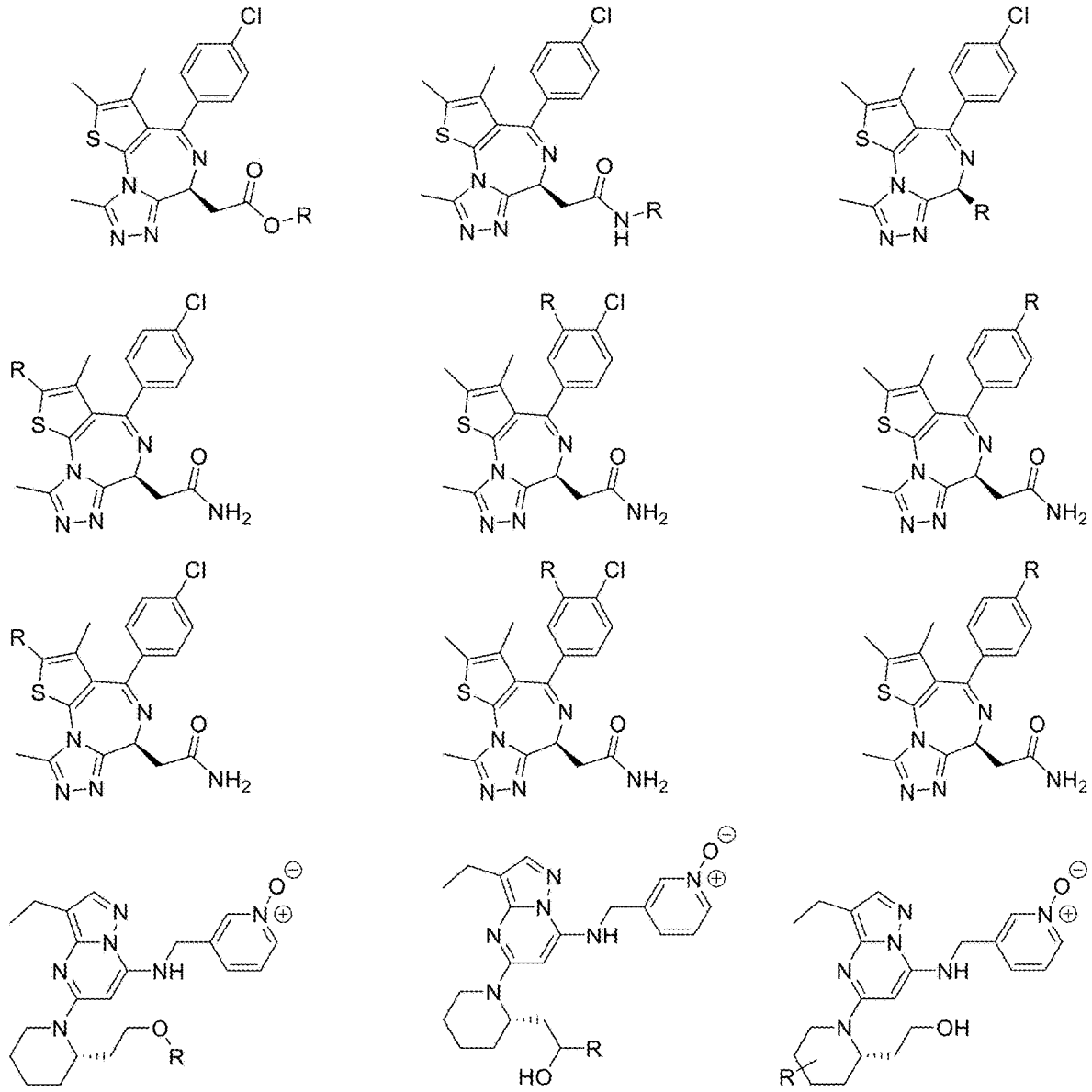


FIG. 3NNN

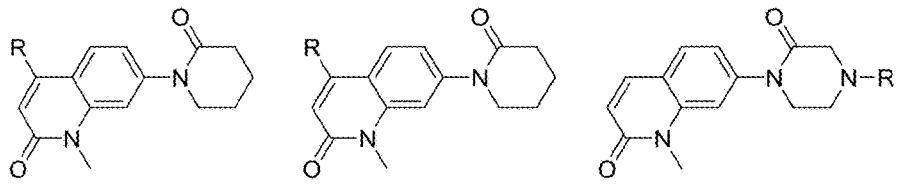


FIG. 3OOO

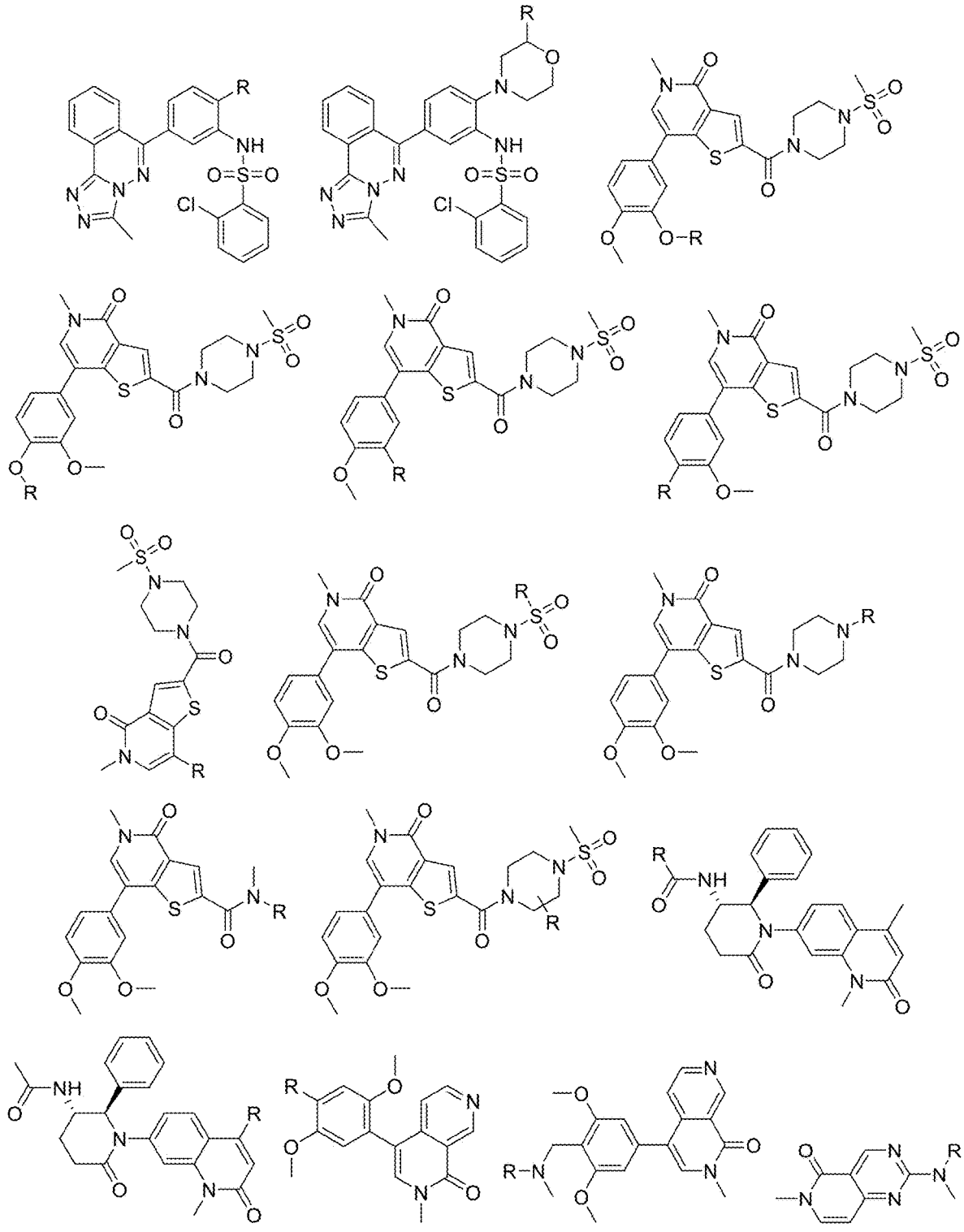


FIG. 3PPP

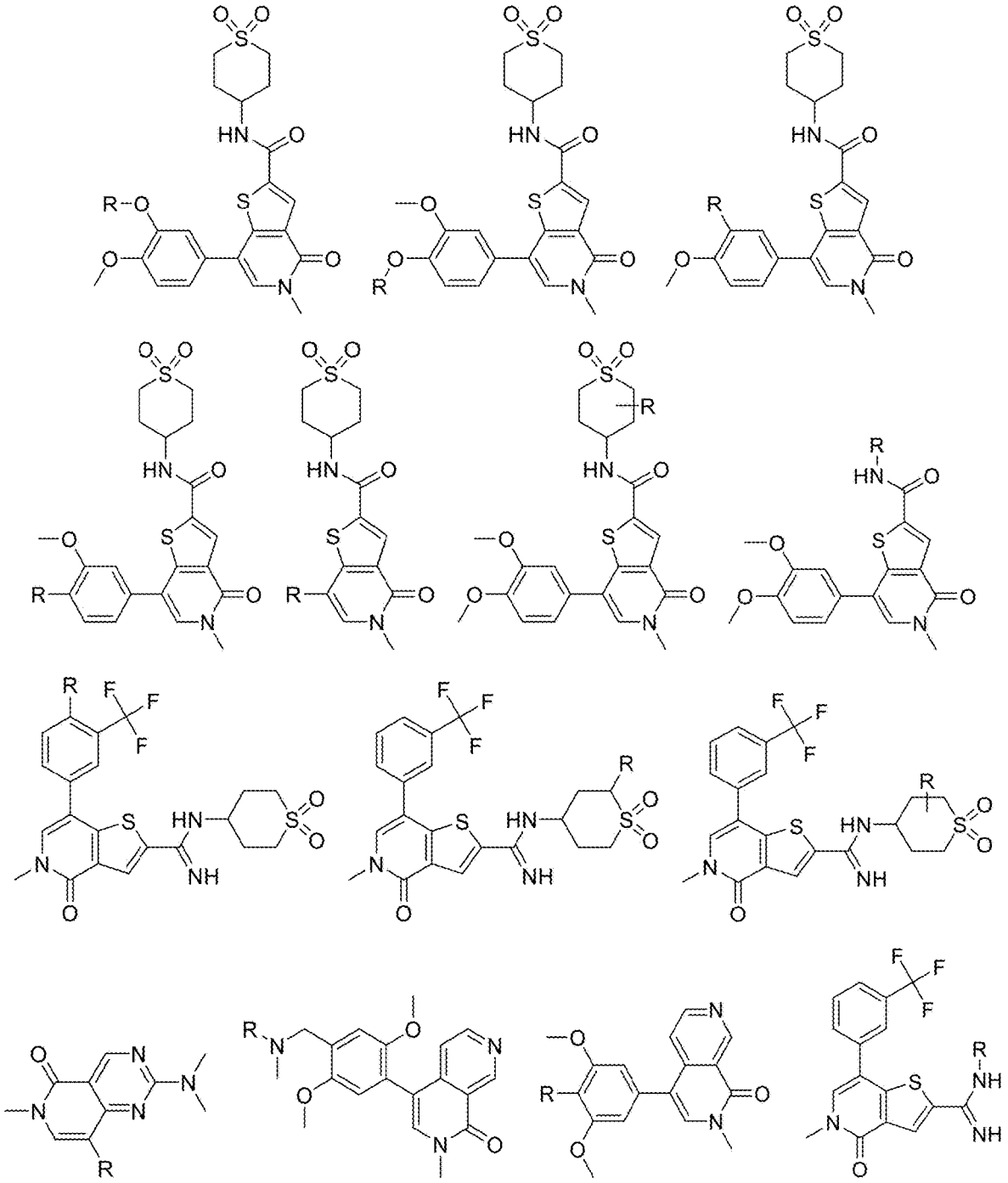


FIG. 3QQQ

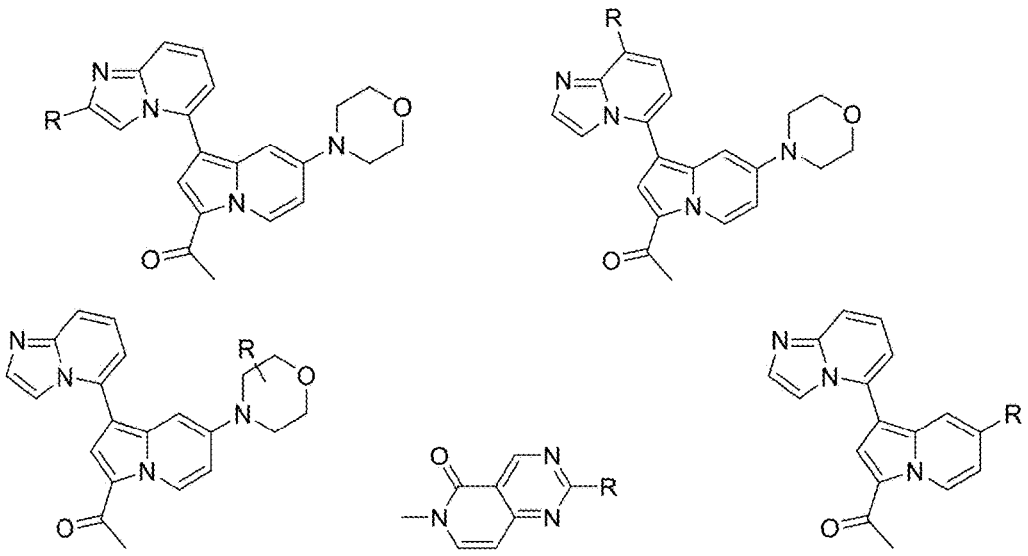


FIG. 3RRR

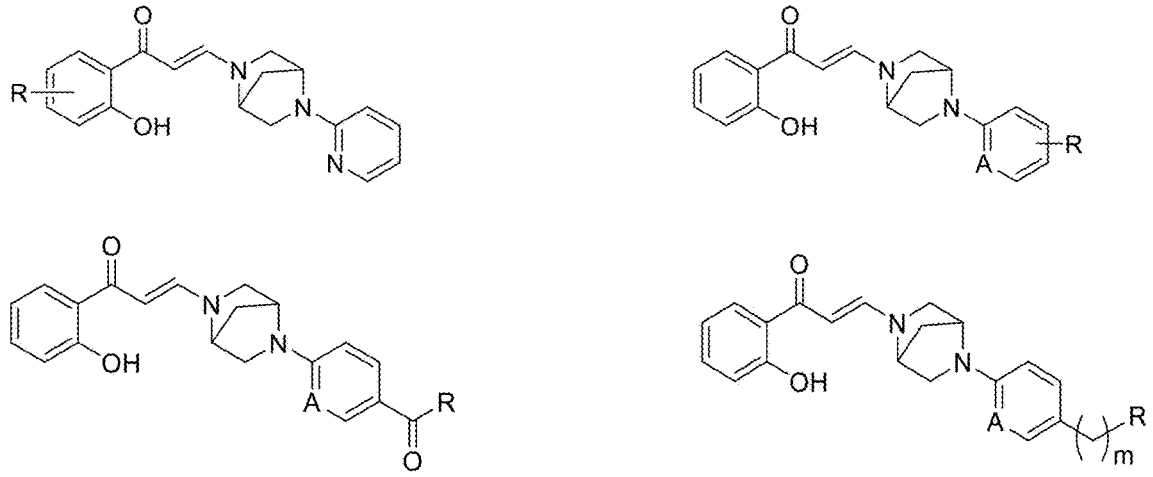


FIG. 3SSS

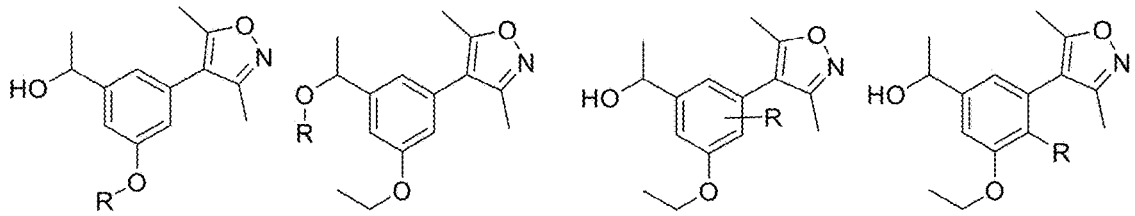


FIG. 3TTT

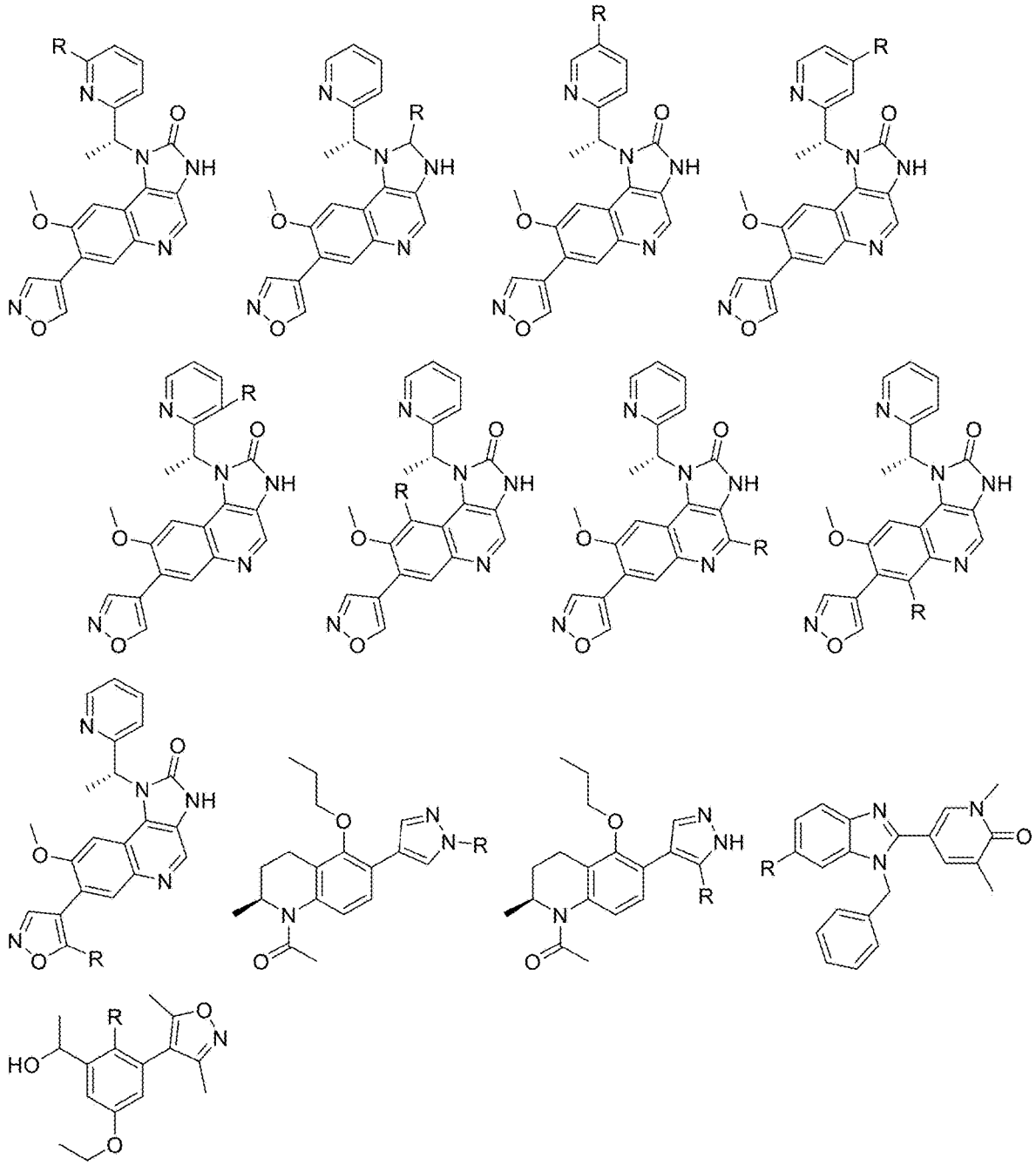


FIG. 3UUU

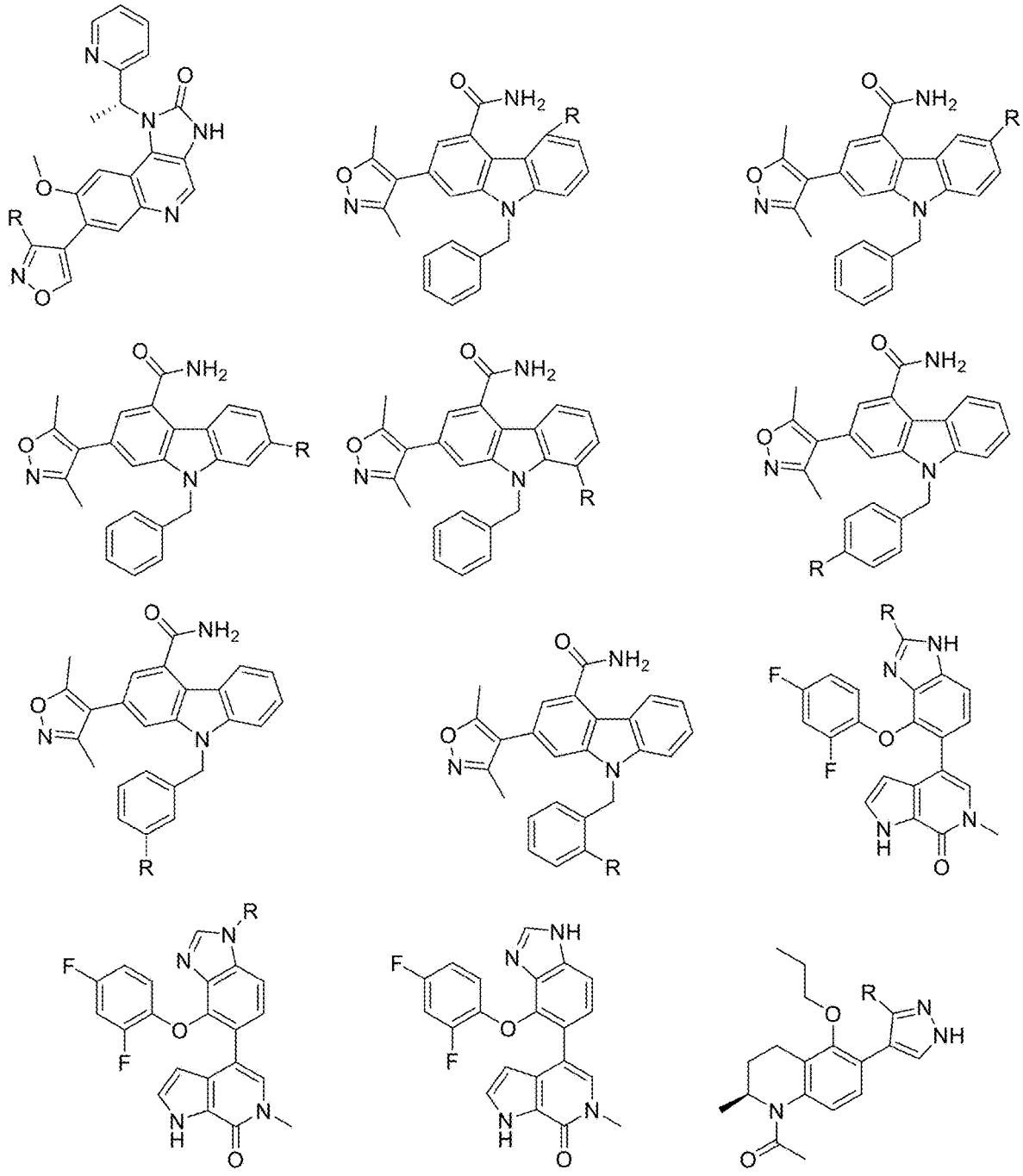


FIG. 3VVV

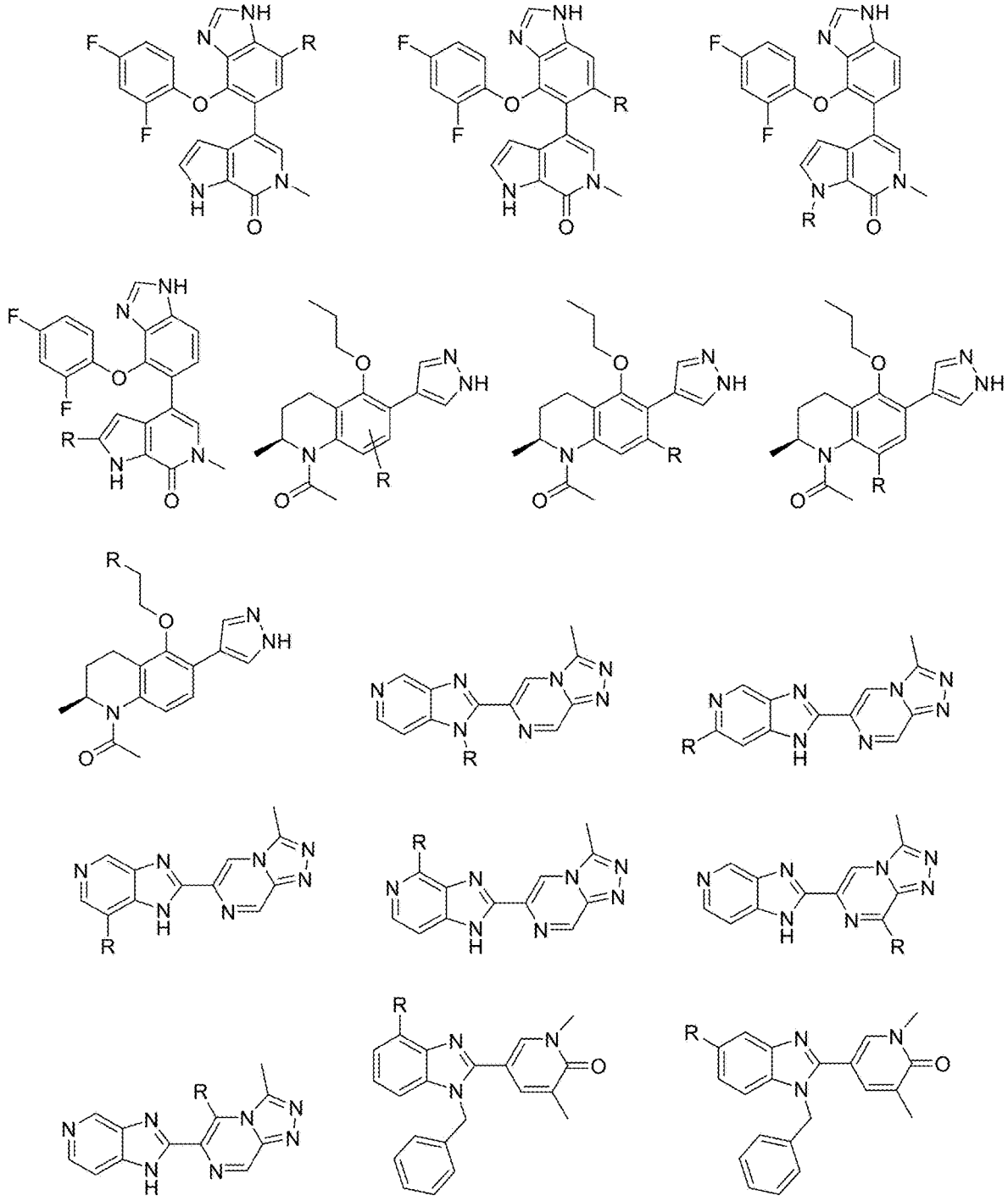


FIG. 3WWW

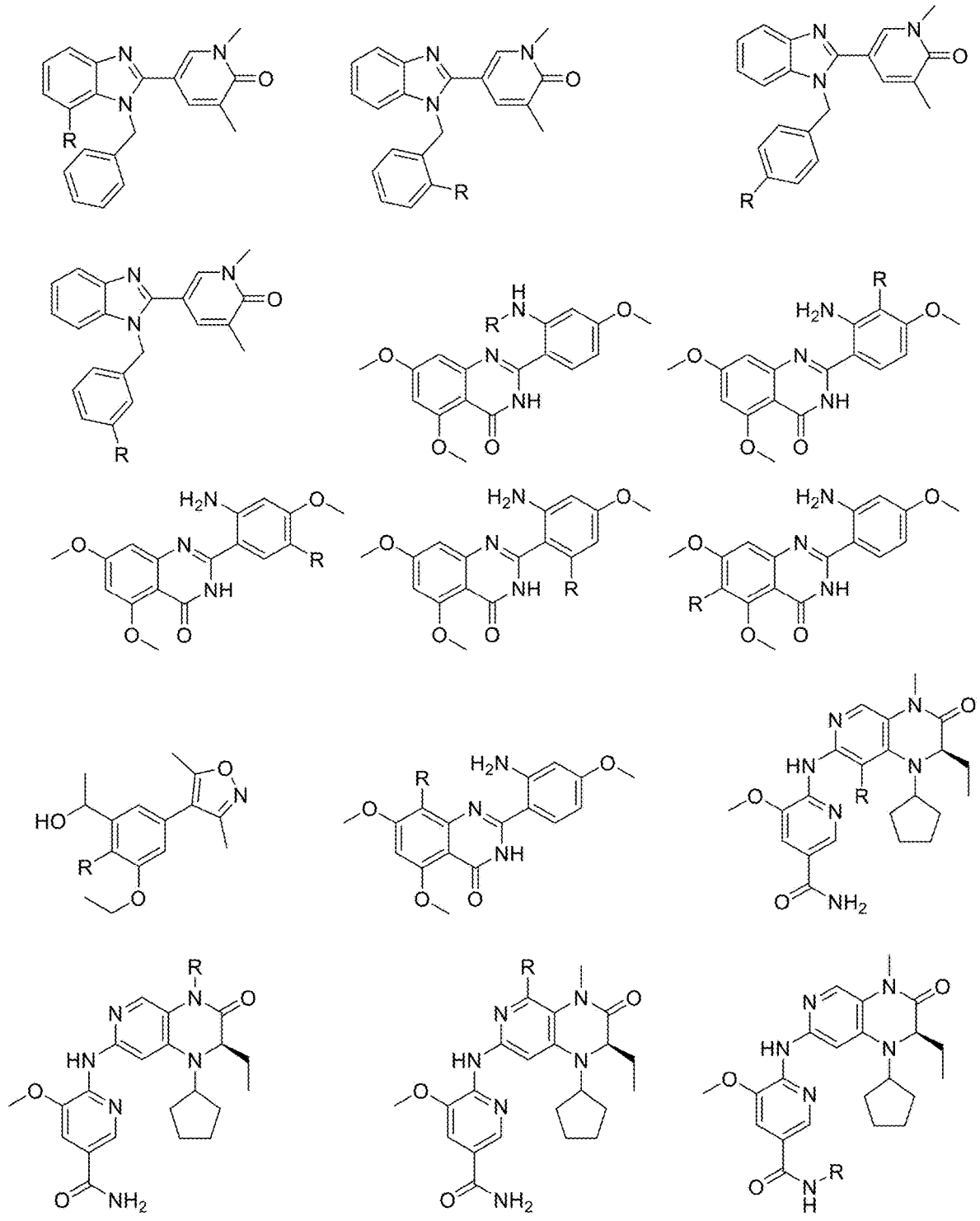


FIG. 3XXX

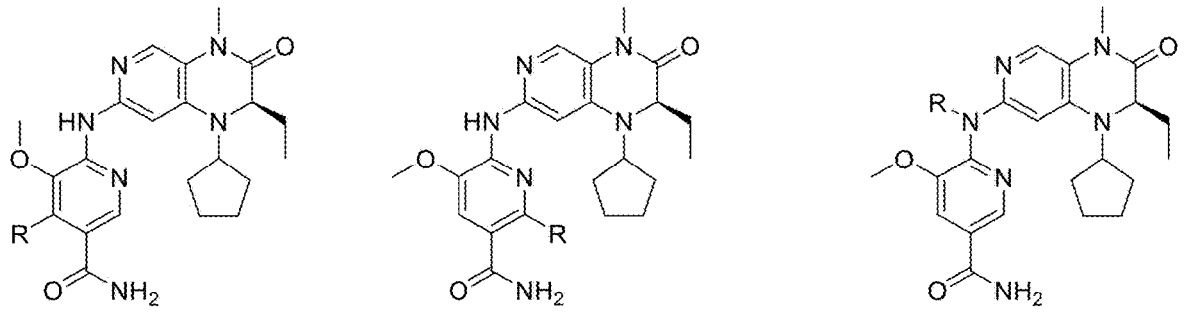


FIG. 3YYY

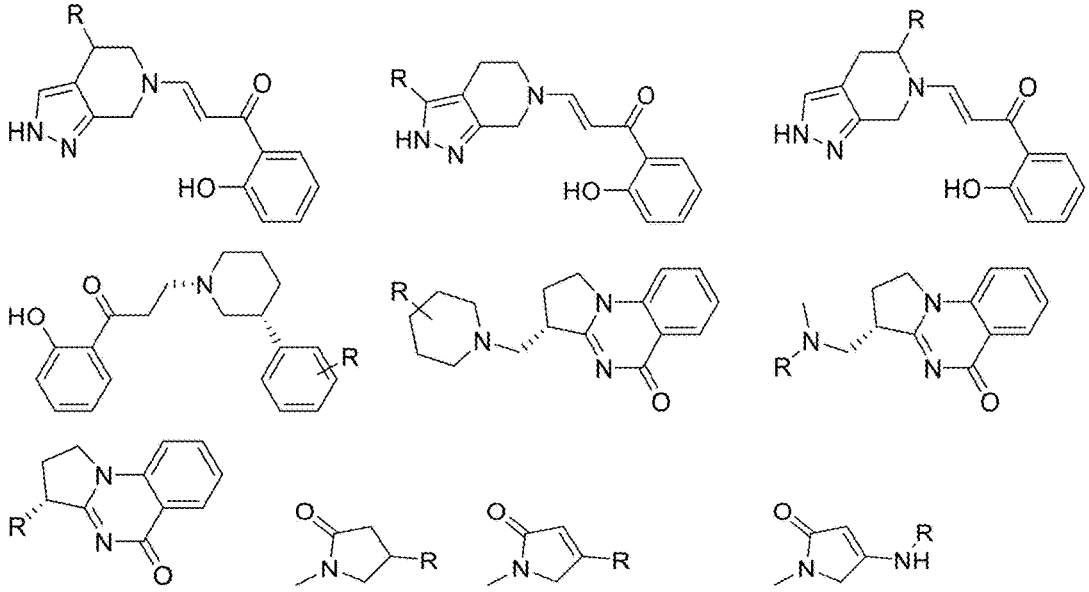


FIG. 3ZZZ

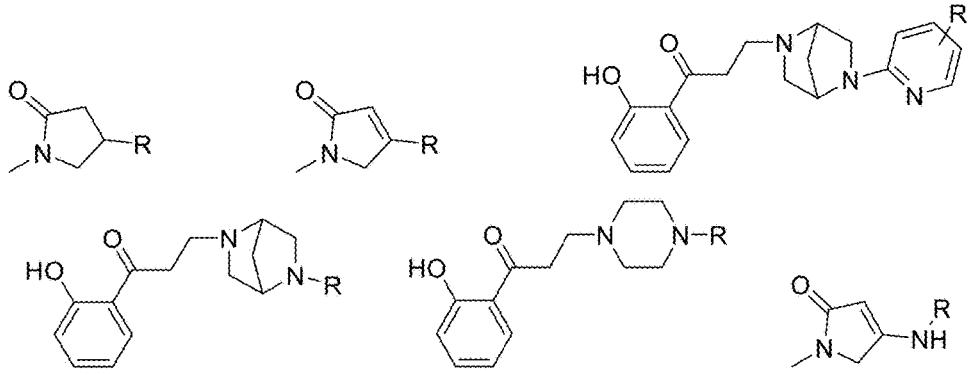
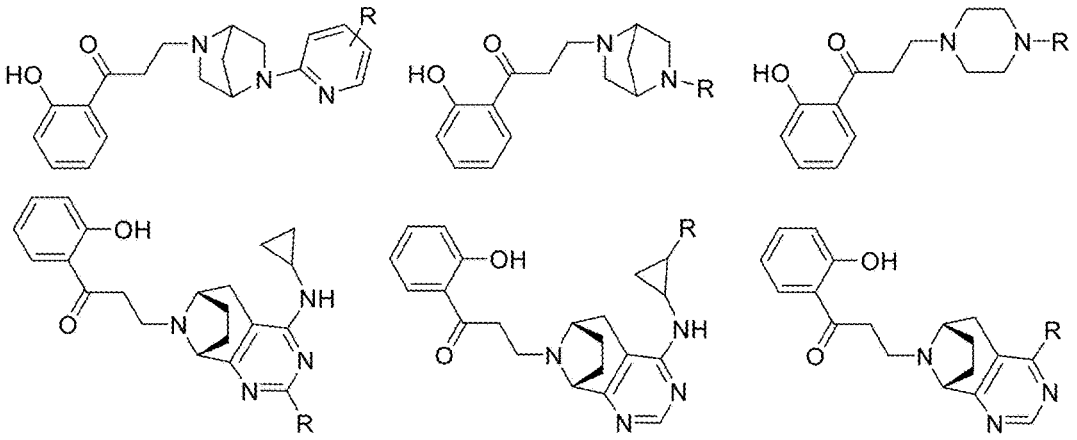


FIG. 3AAAA



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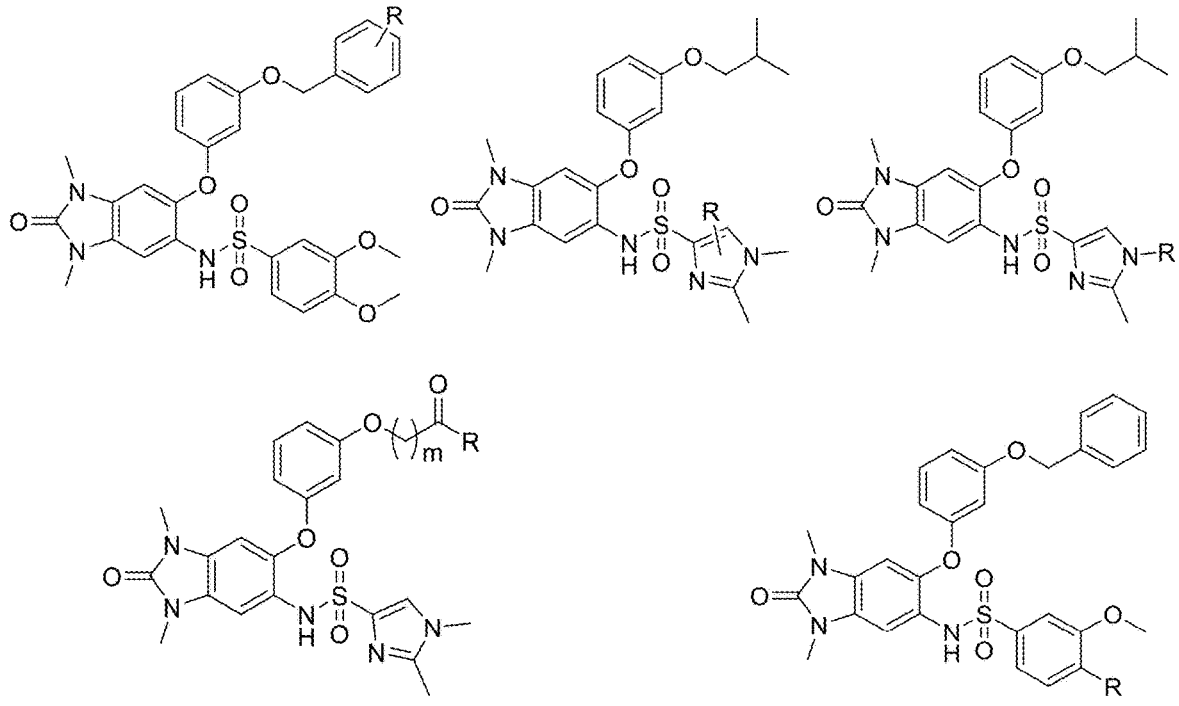
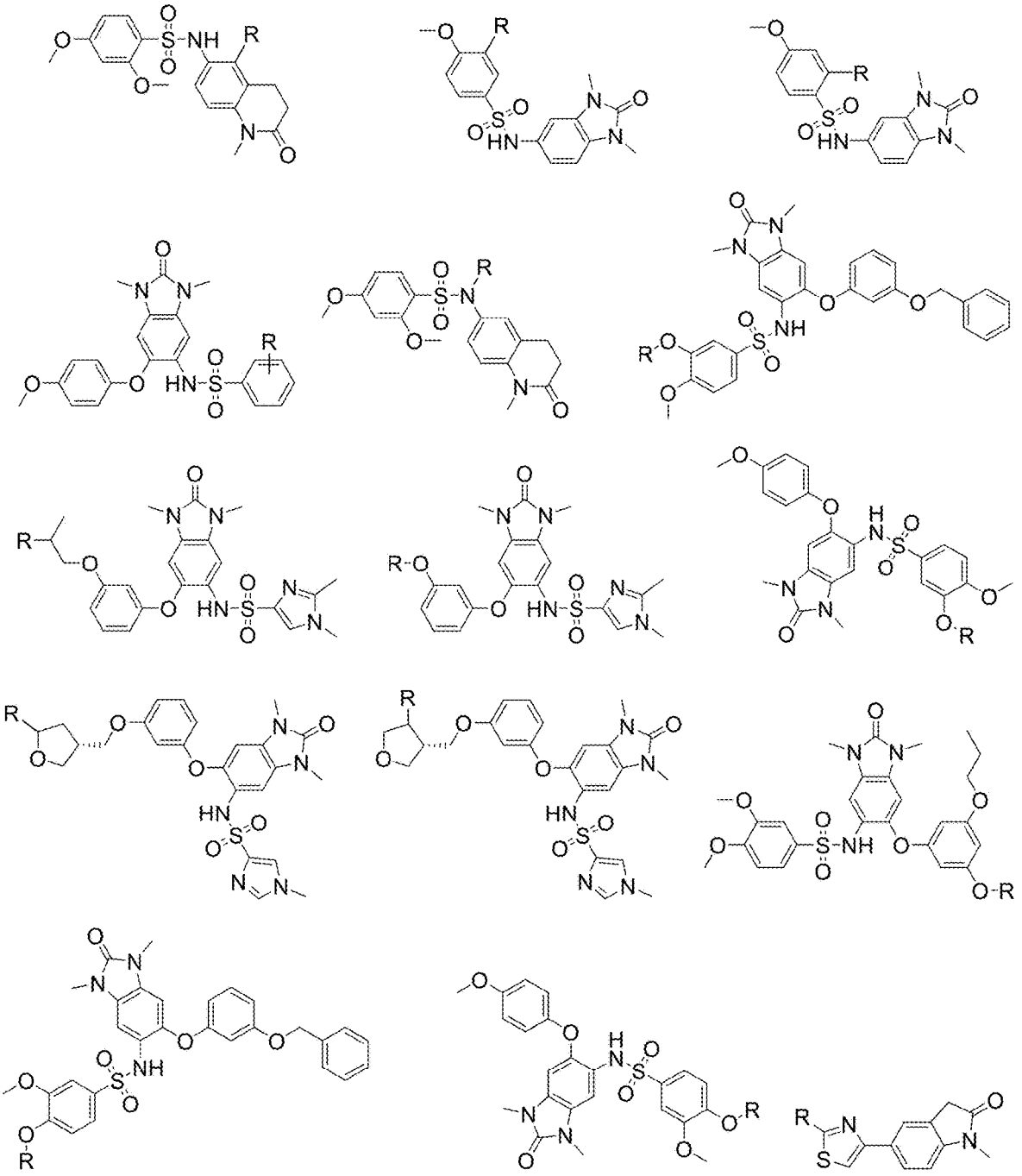


FIG. 3CCCC



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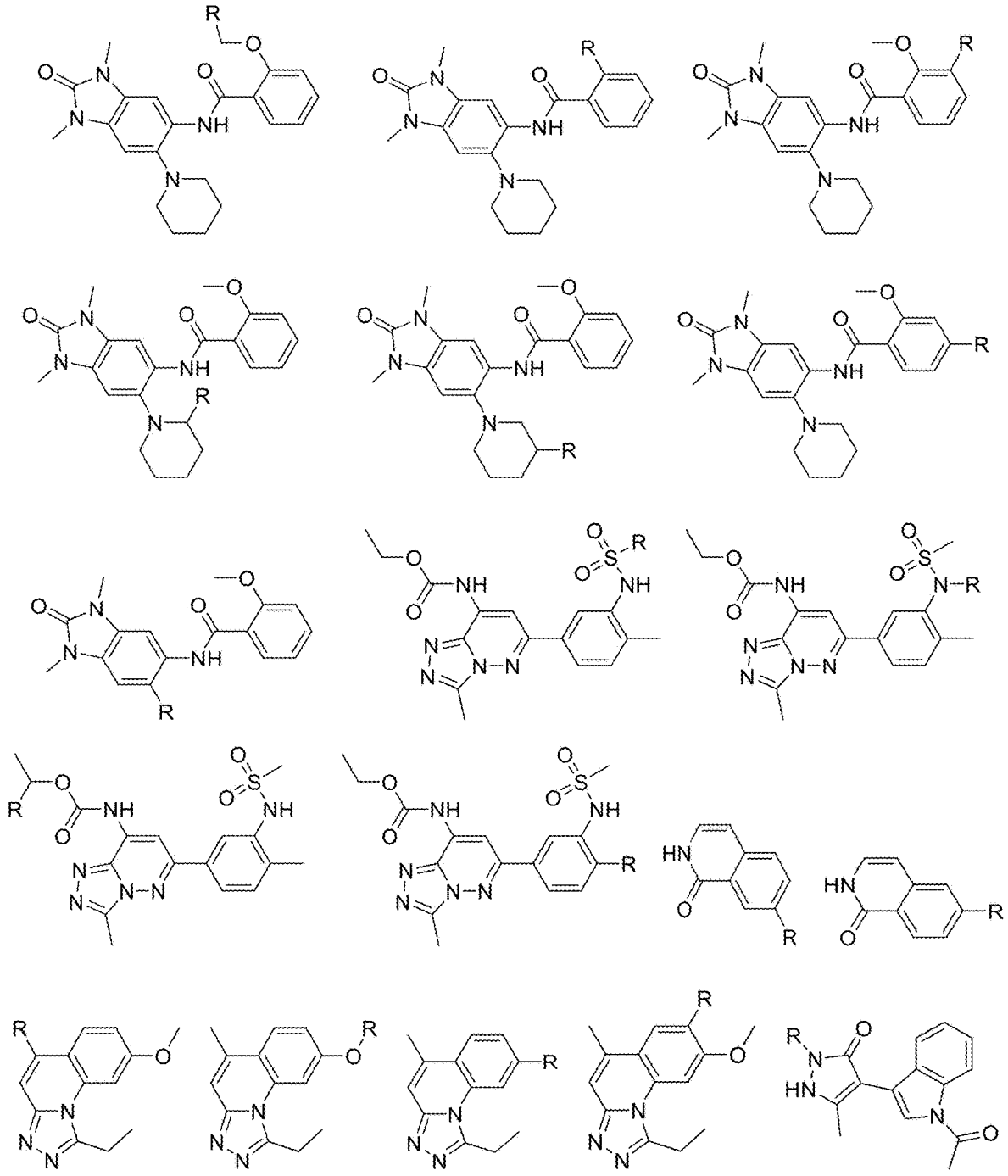


FIG. 3EEEE

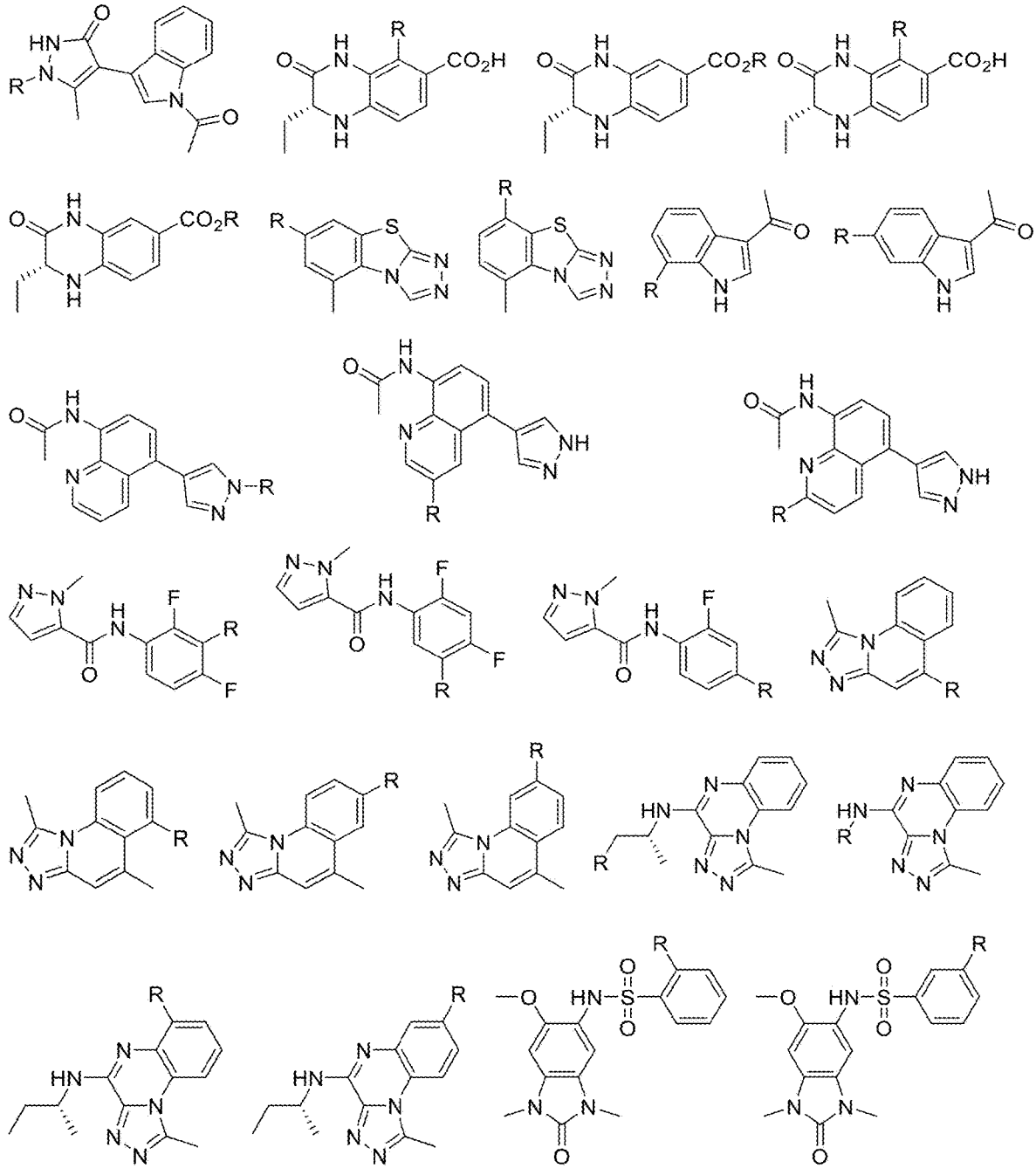


FIG. 3FFFF

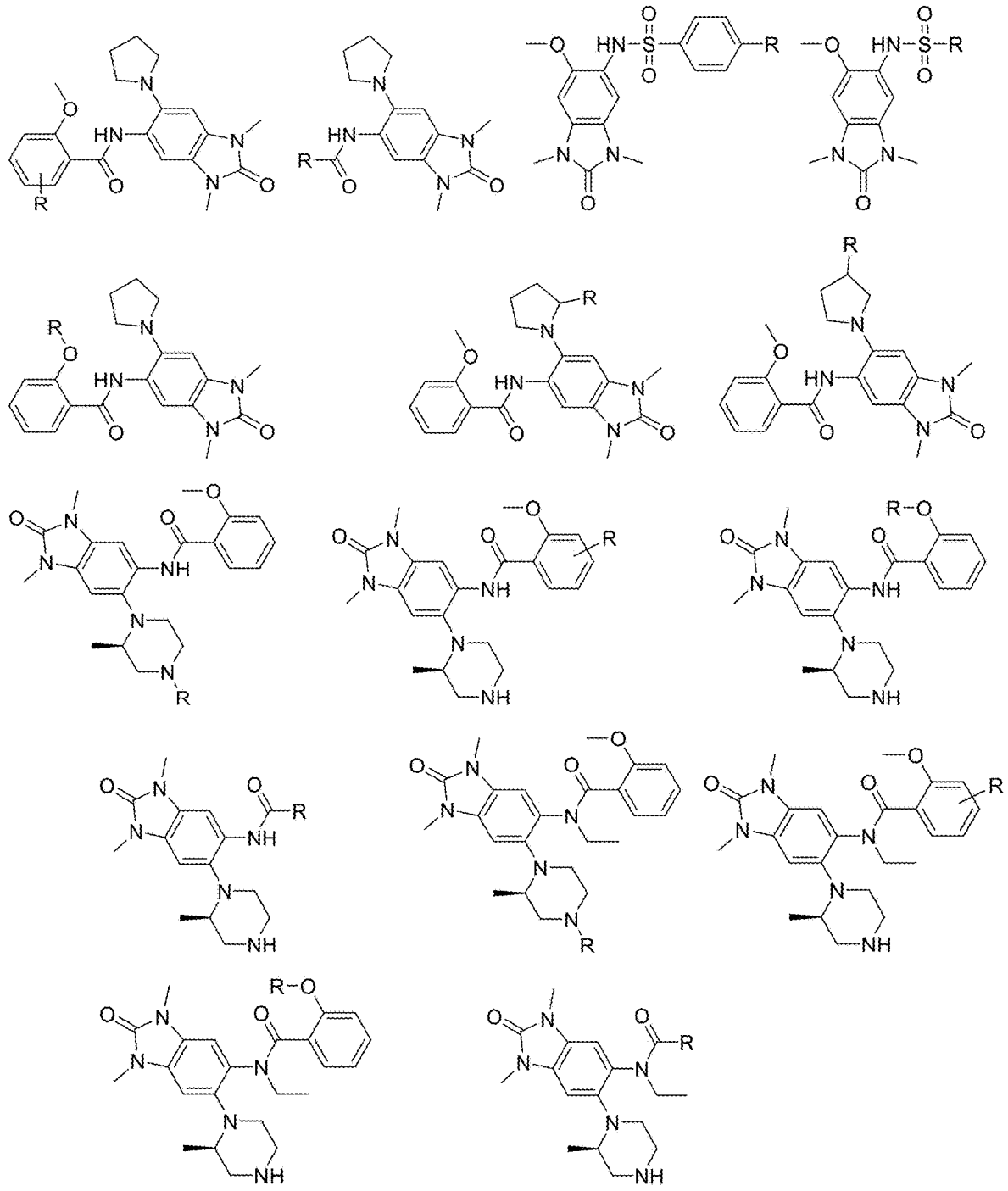


FIG. 3GGGG

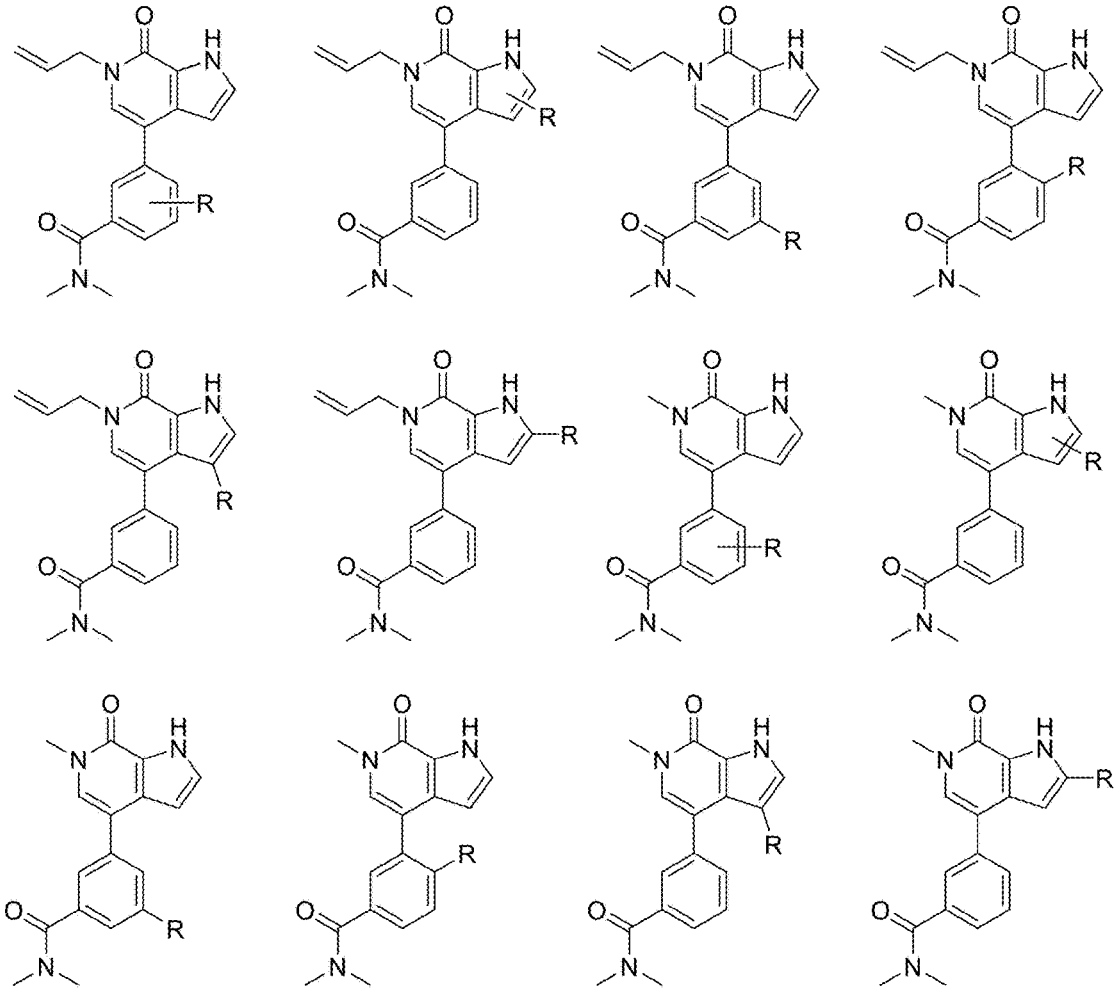


FIG. 3HHHH

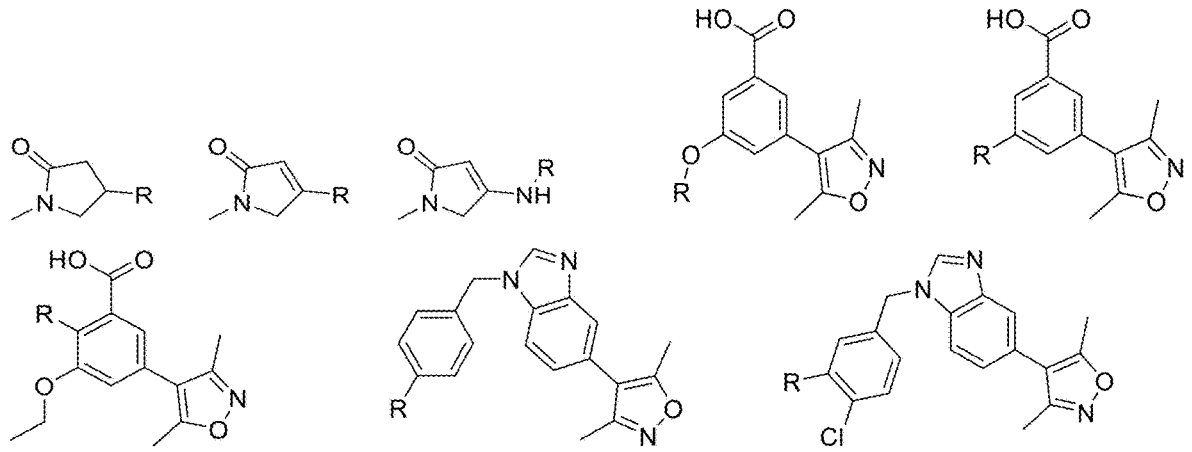


FIG. 3IIII

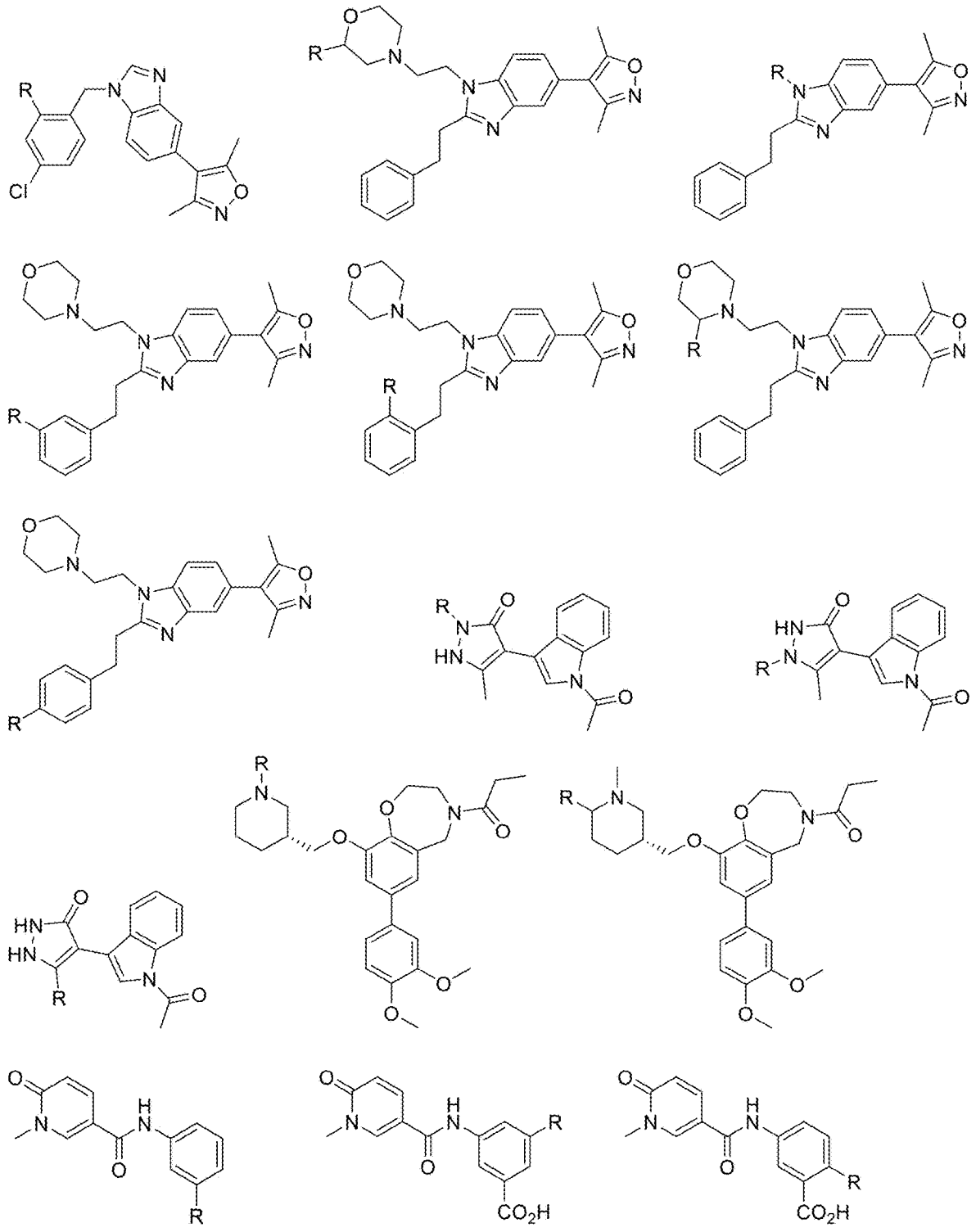


FIG. 3JJJJ

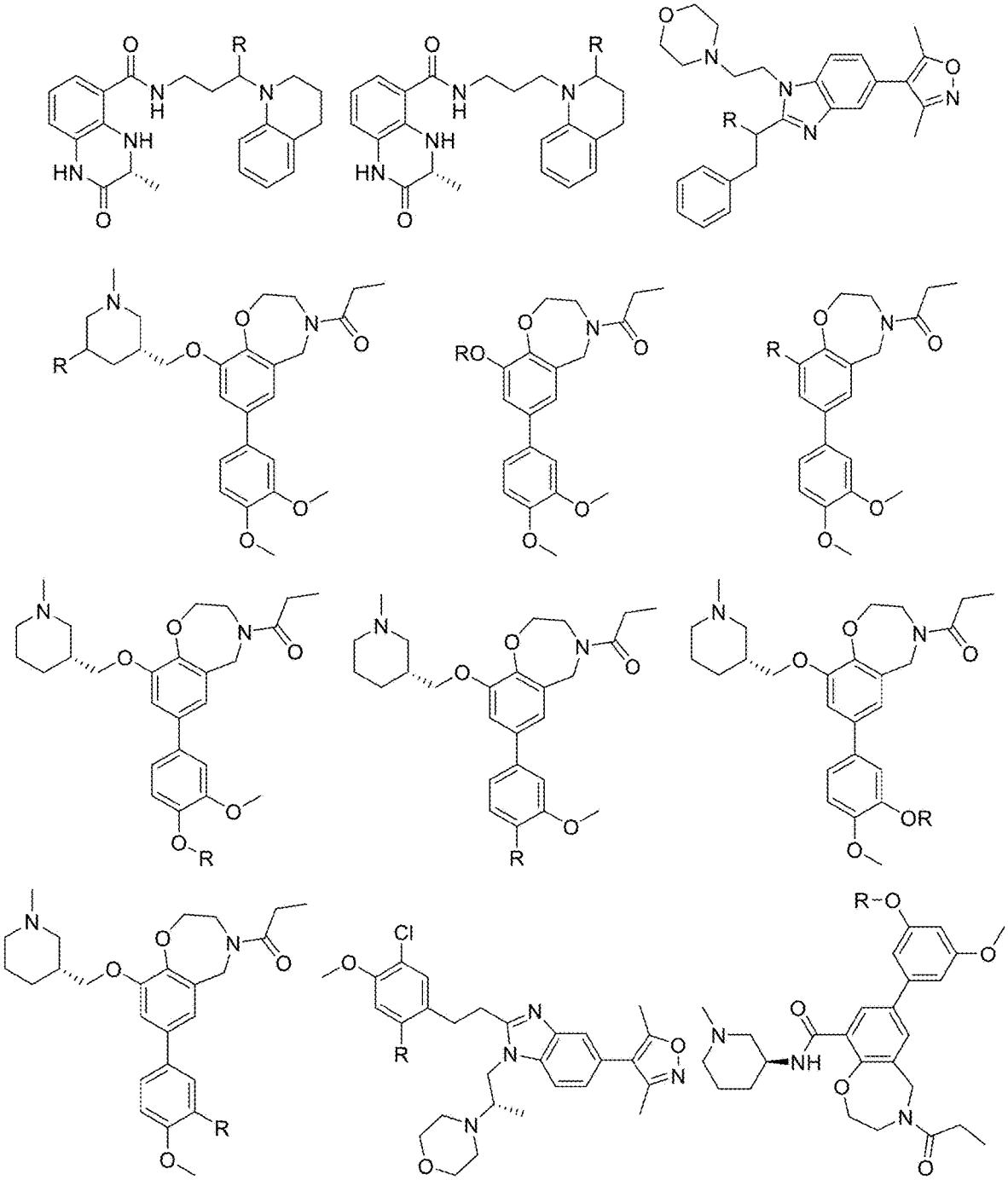


FIG. 3KKKK

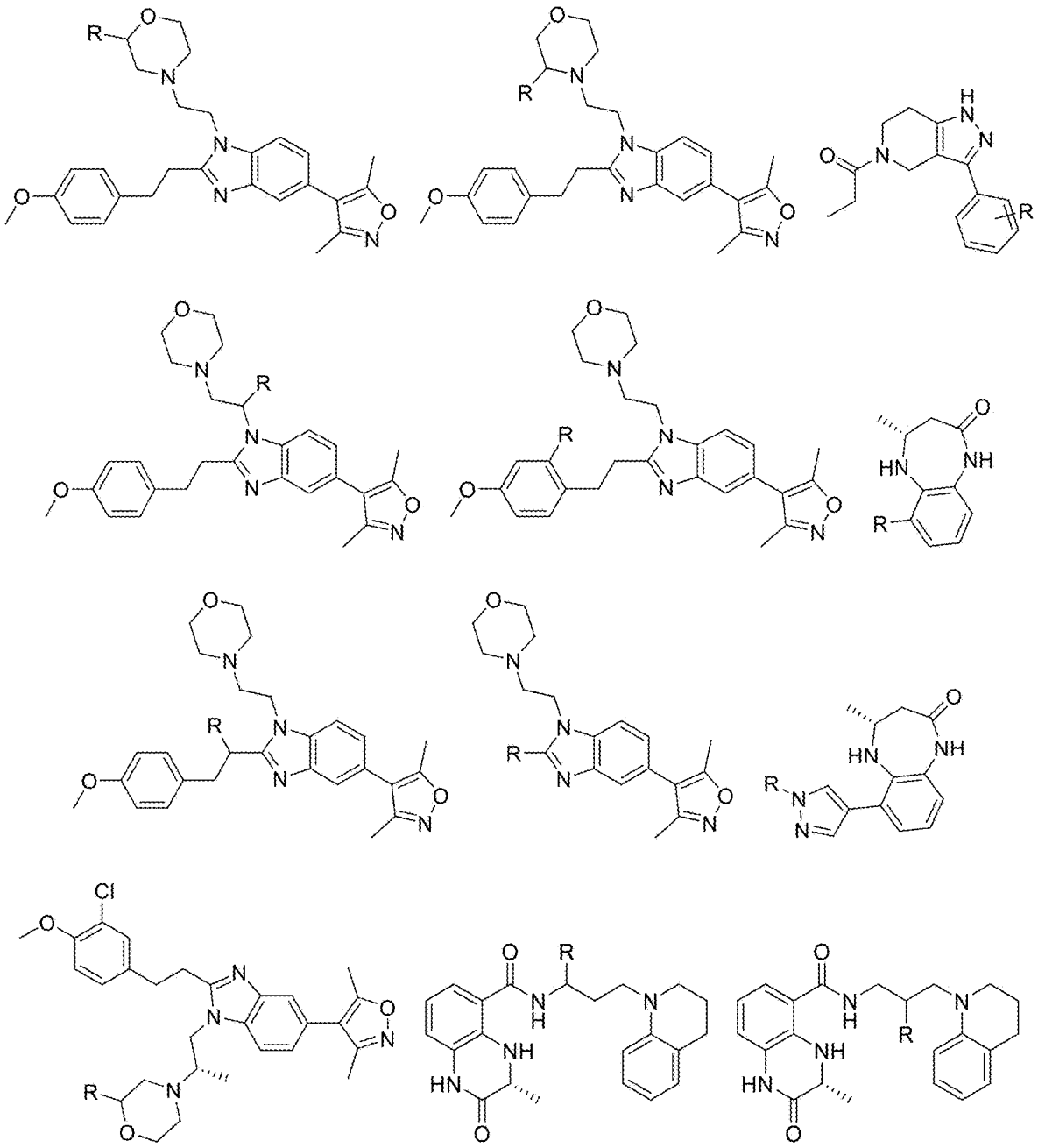


FIG. 3LLLL

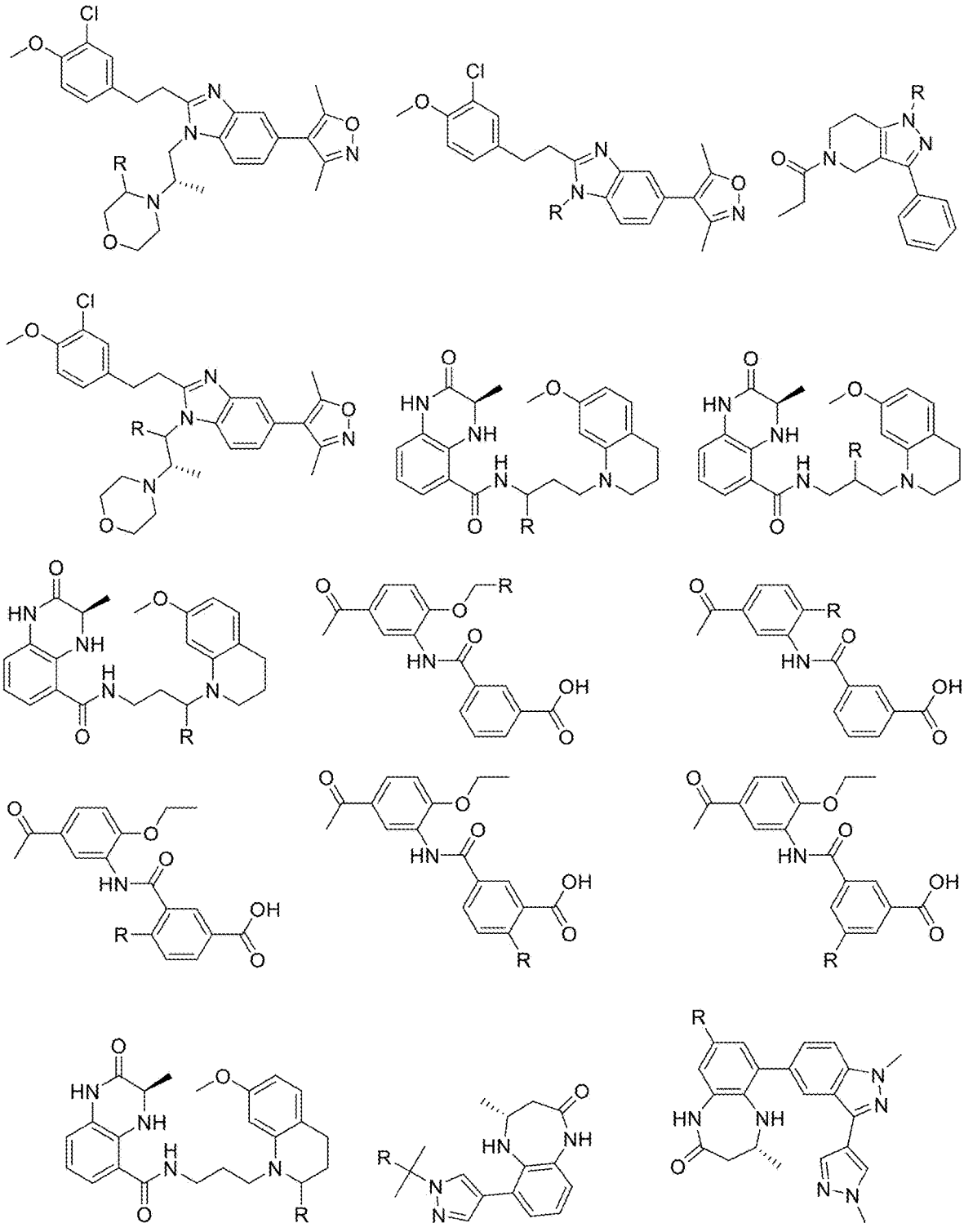


FIG. 3MMMM

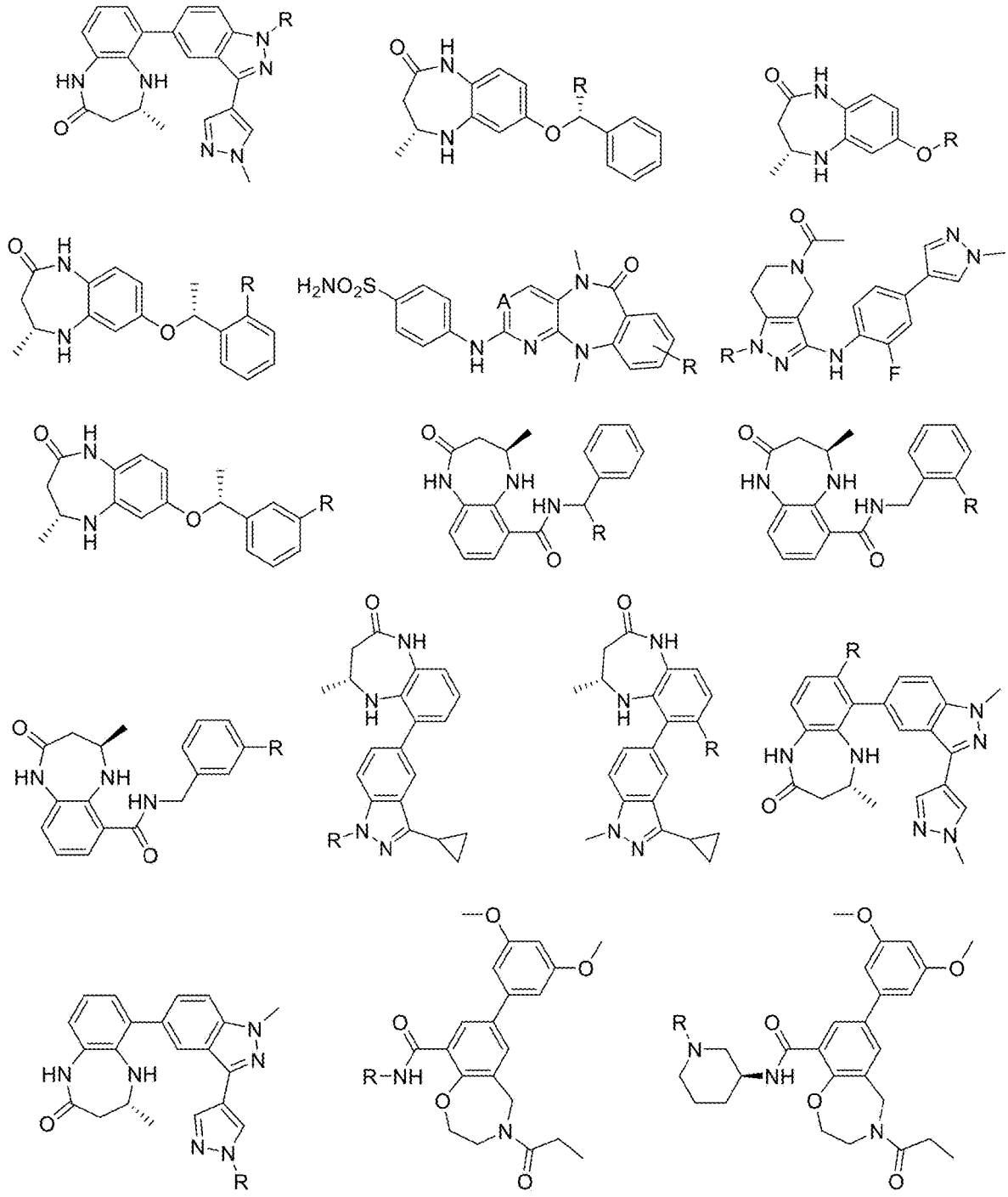


FIG. 3NNNN

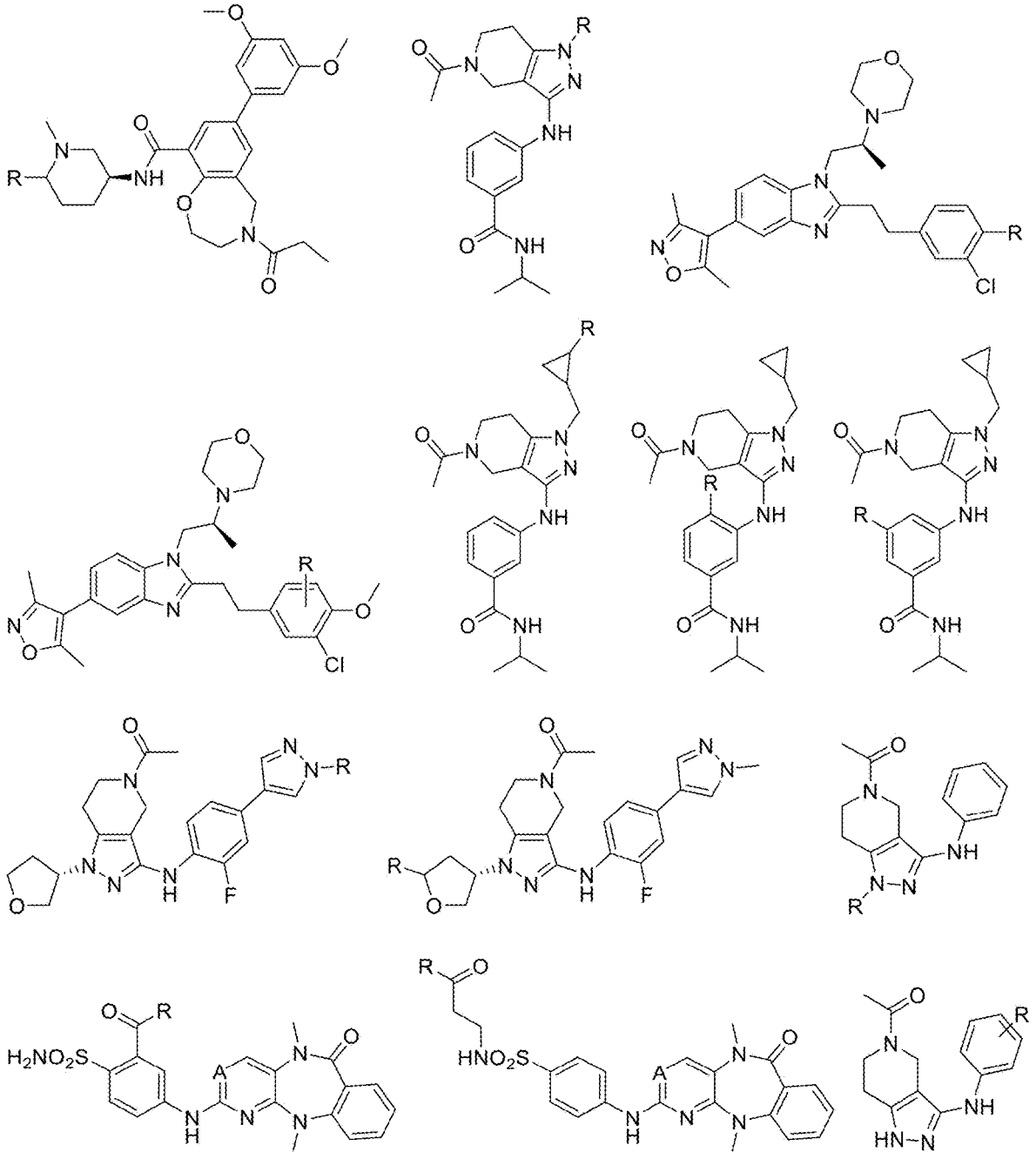


FIG. 3OOOO

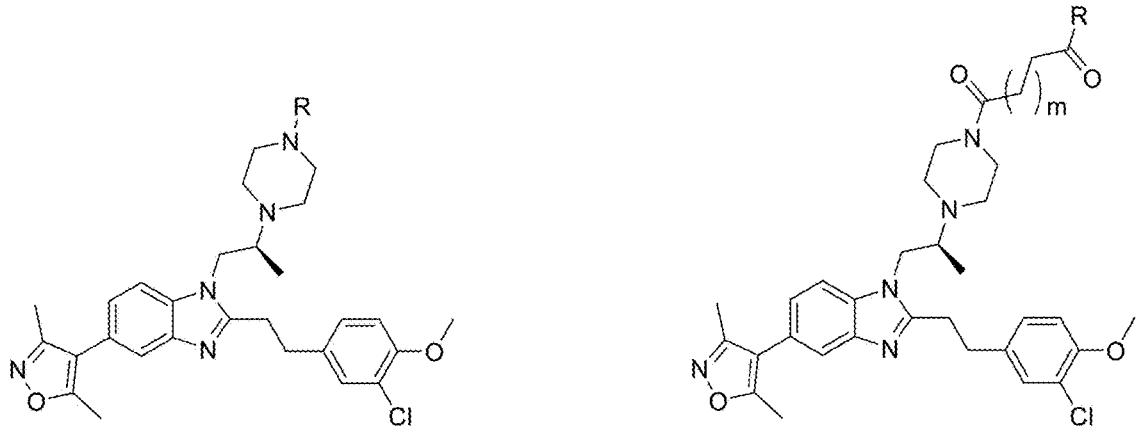
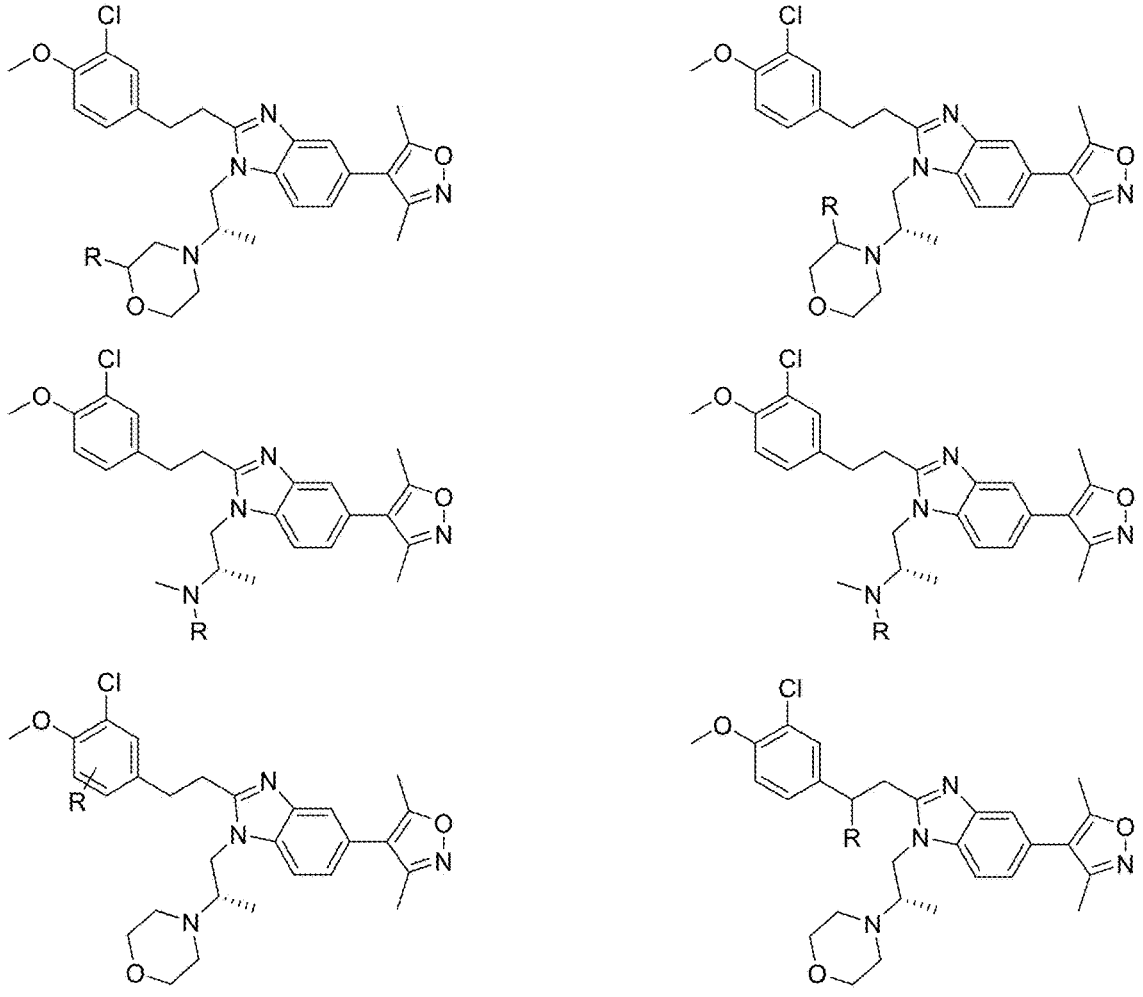


FIG. 3PPPP



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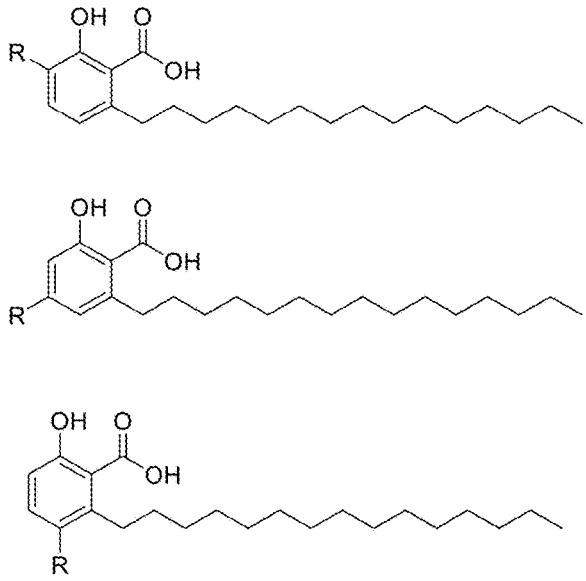

FIG. 3RRRR

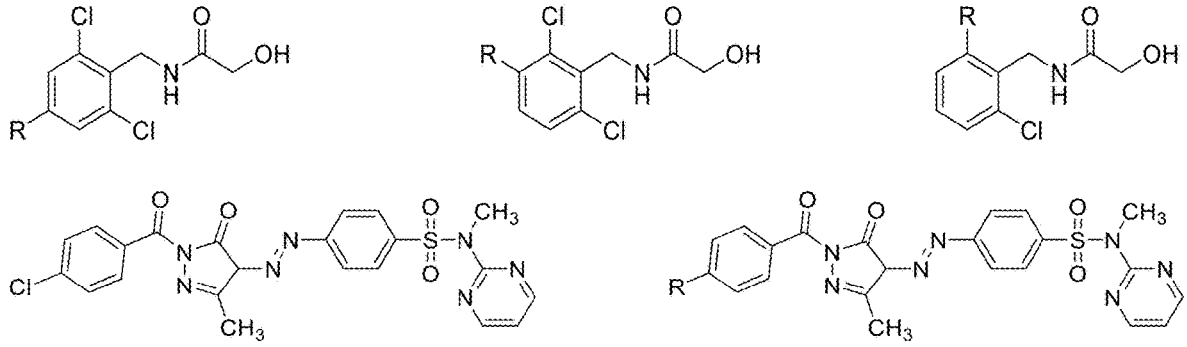

FIG. 3SSSS

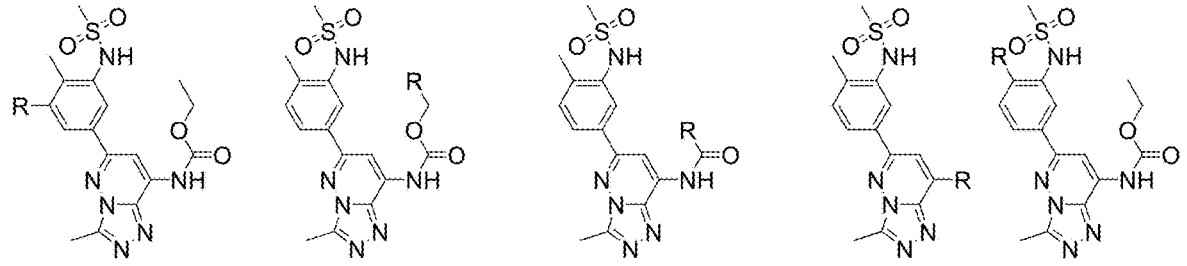

FIG. 3TTTT

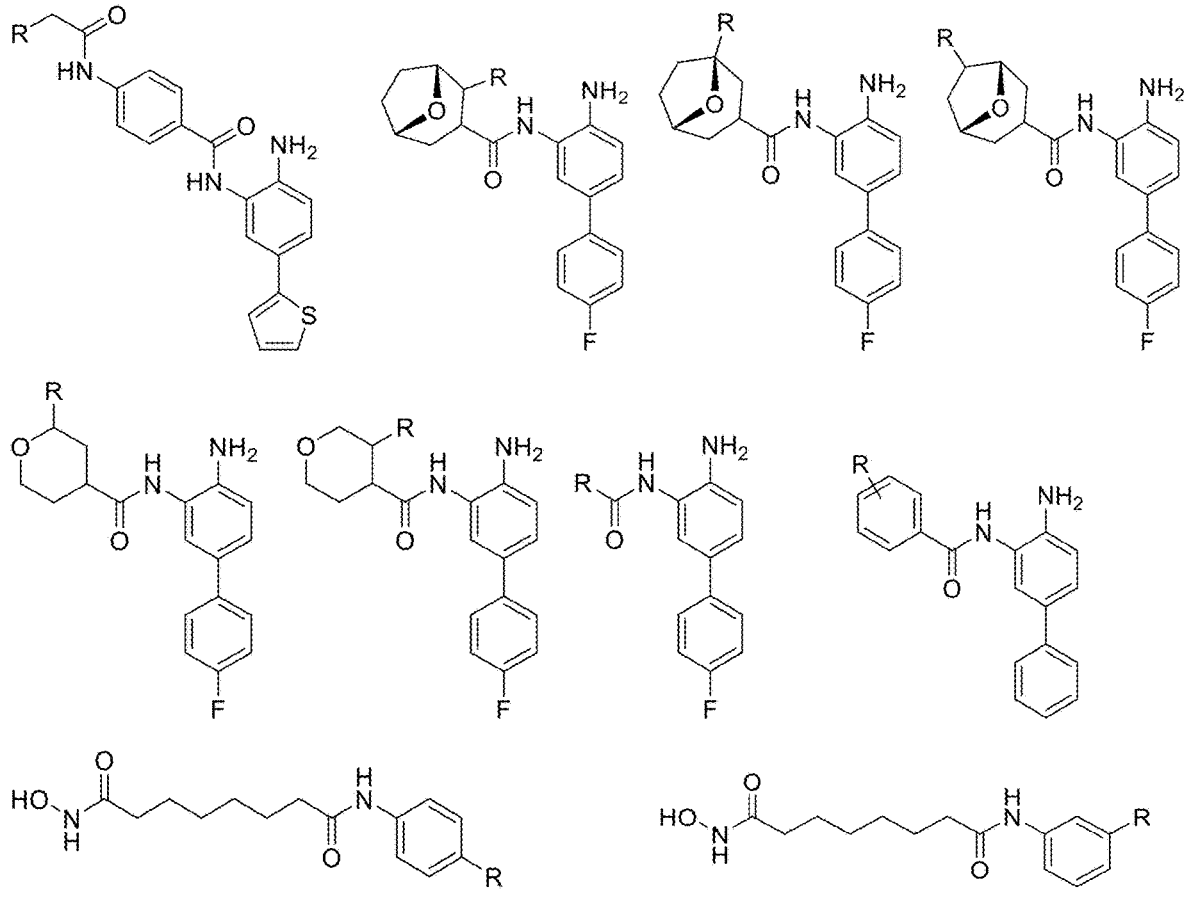

FIG. 3UUUU

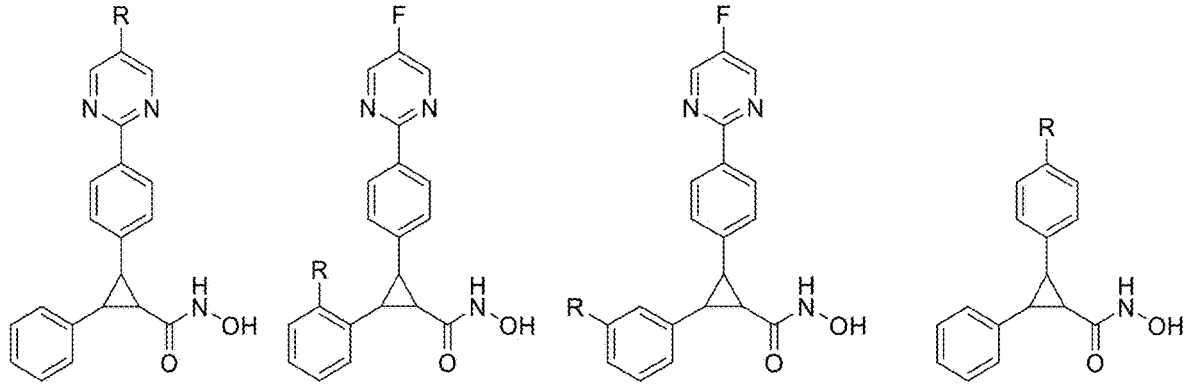

FIG. 3VVVV

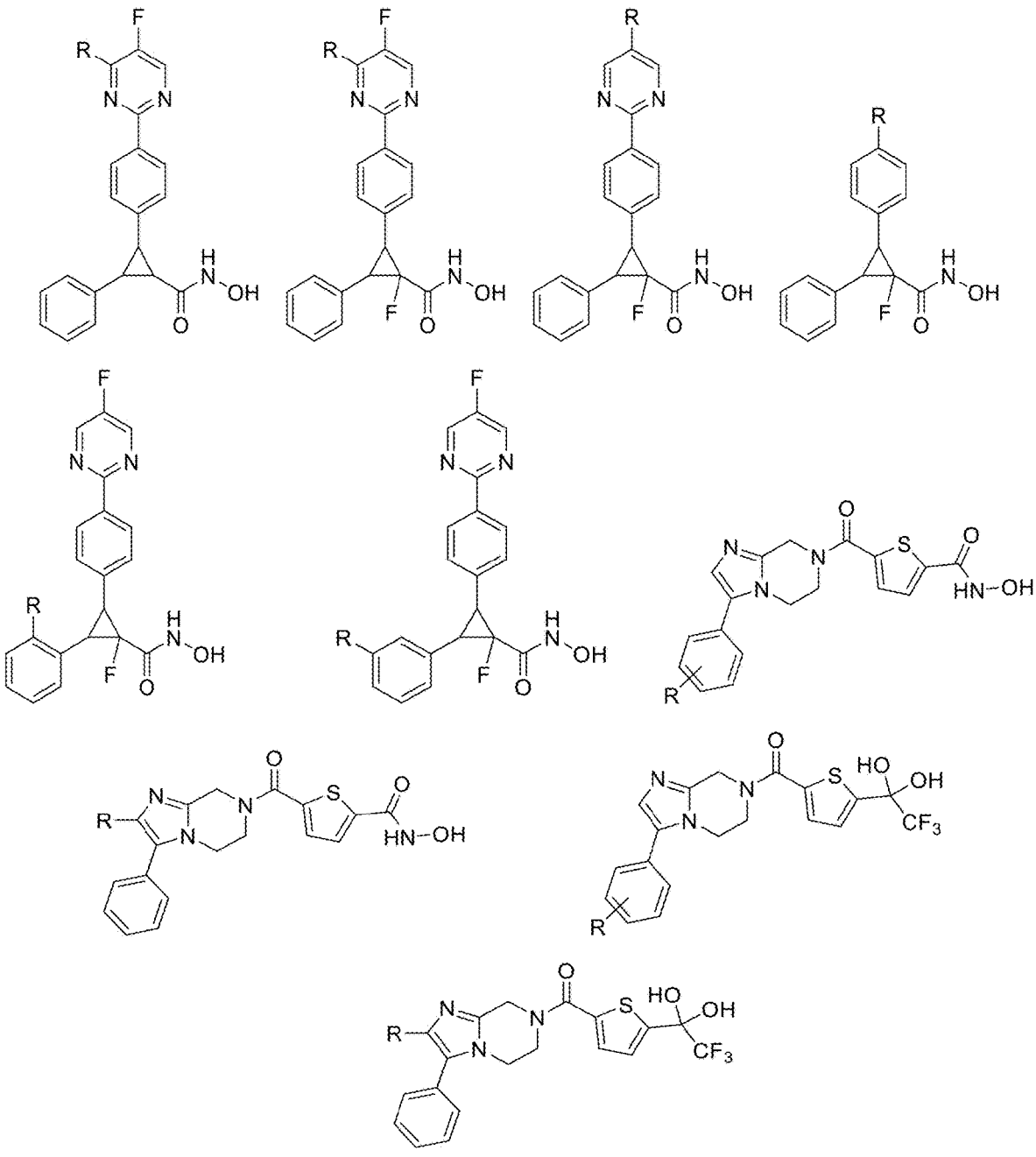

FIG. 3WWWW

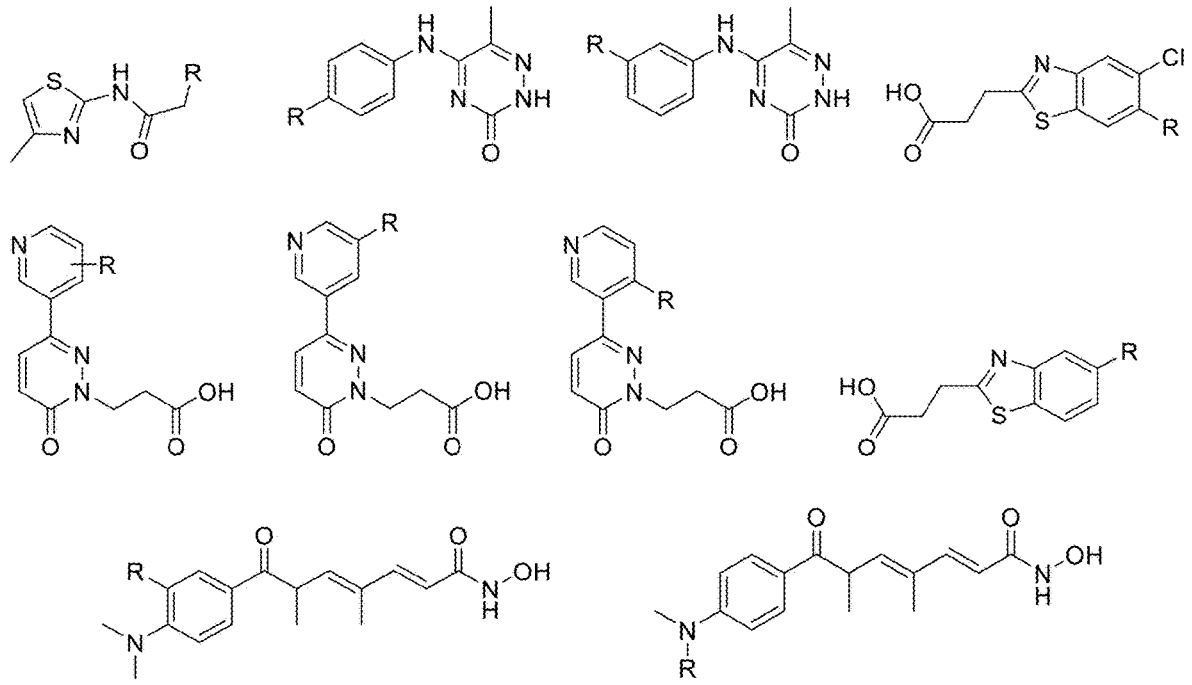

FIG. 3XXXX

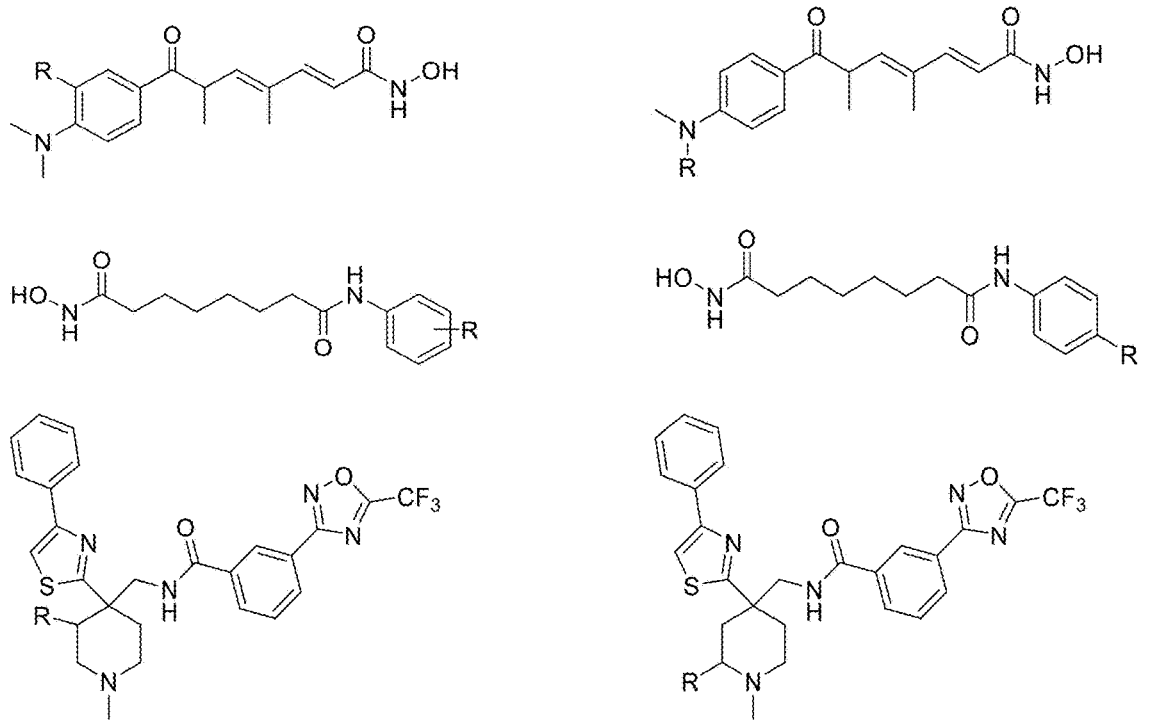

FIG. 3YYYY

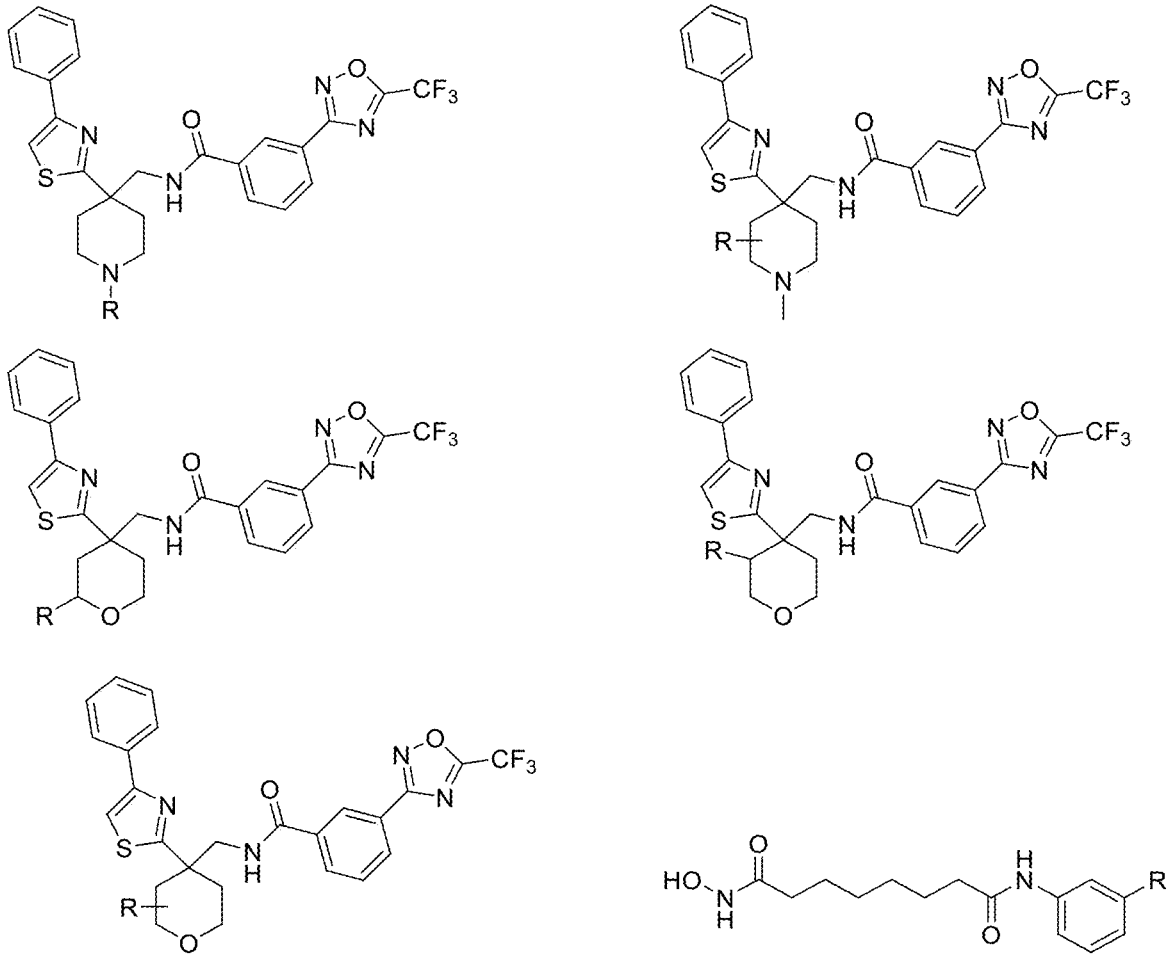

FIG. 3ZZZZ

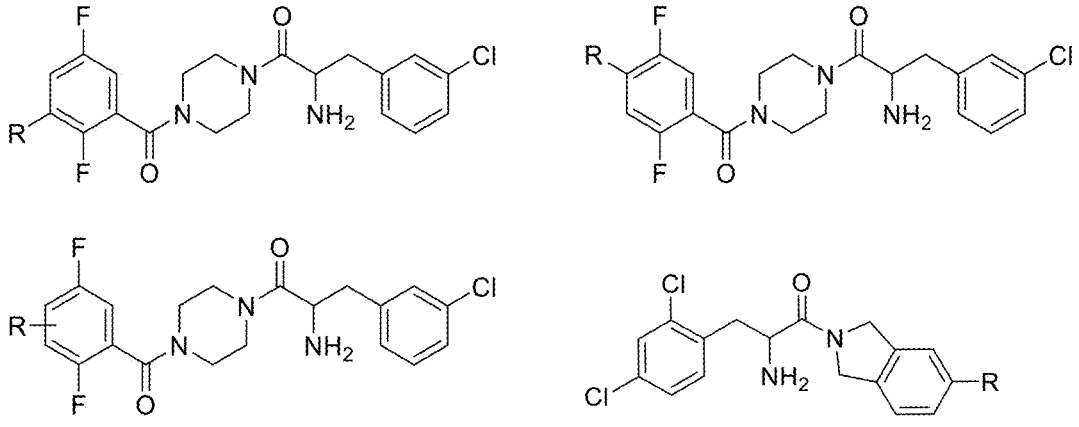

FIG. 3AAAAA

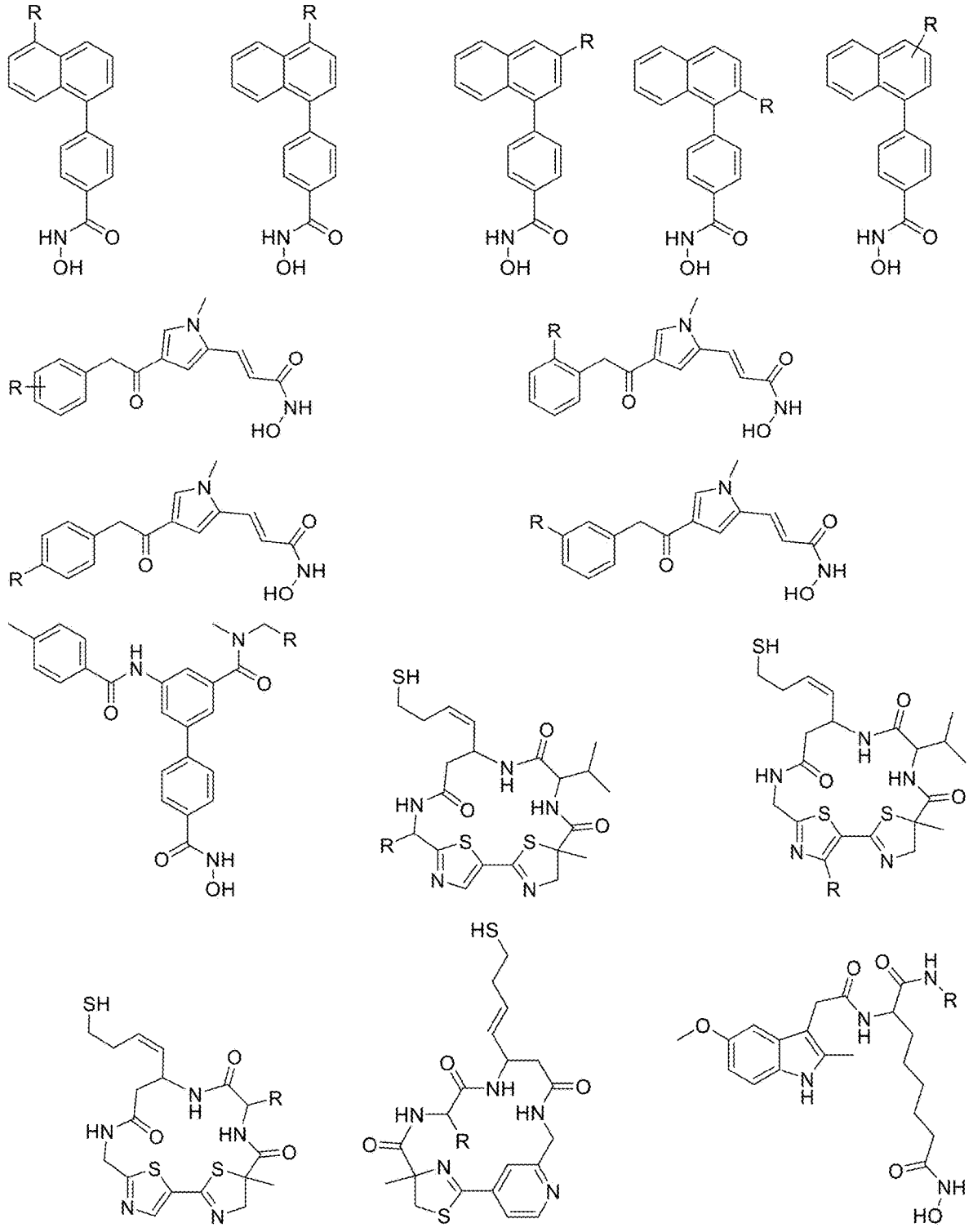

FIG. 3BBBBB

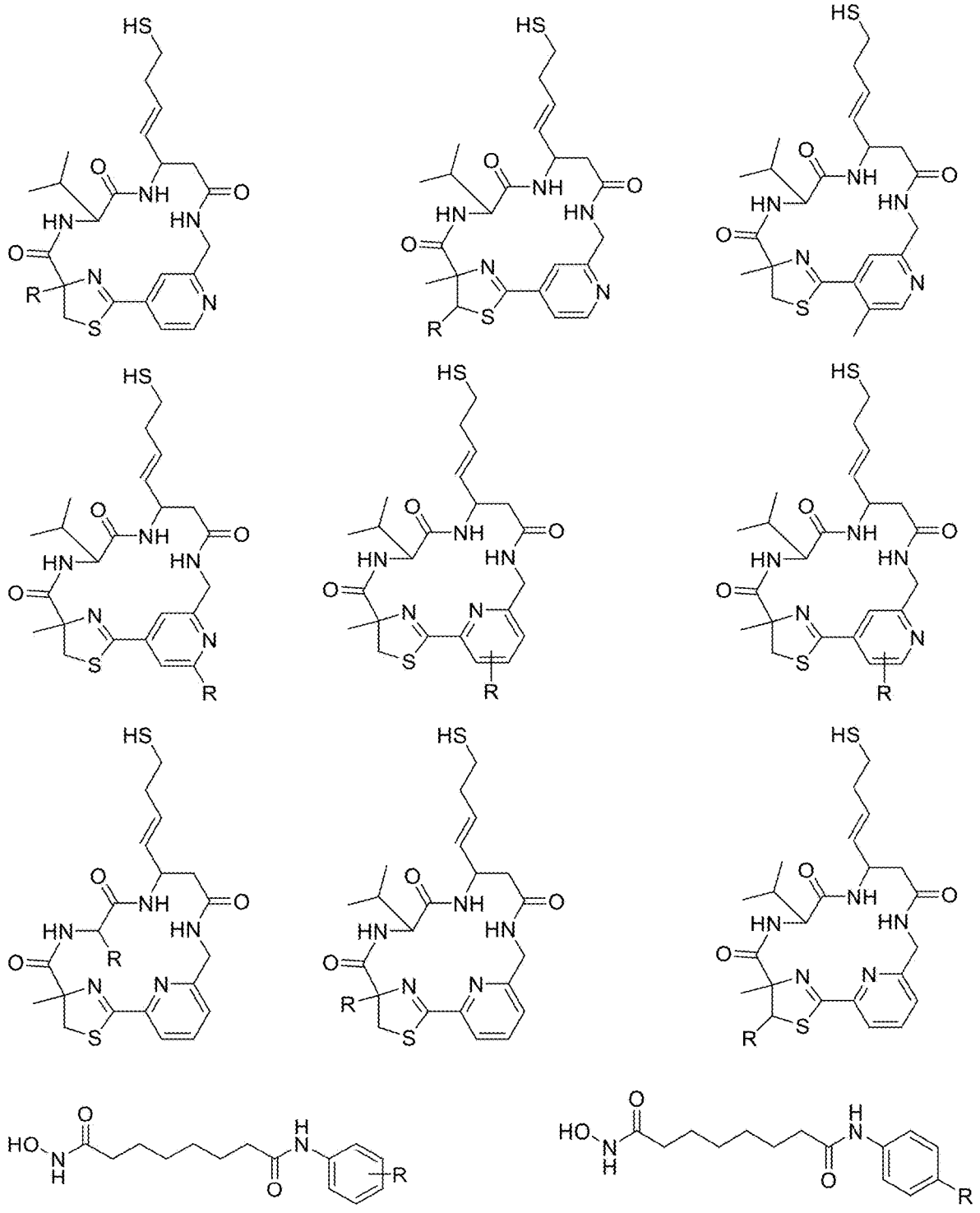

FIG. 3CCCCC

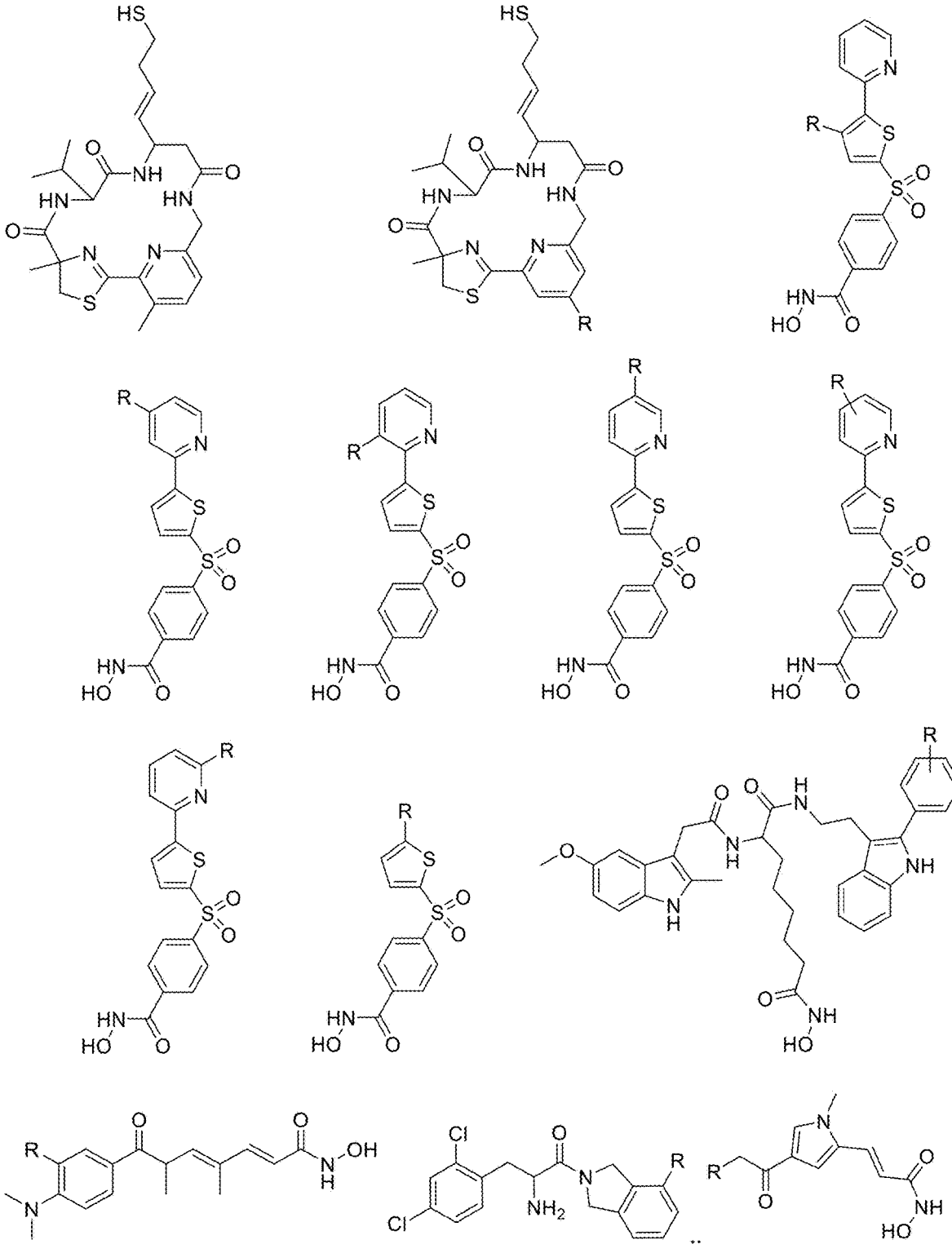

FIG. 3DDDDD

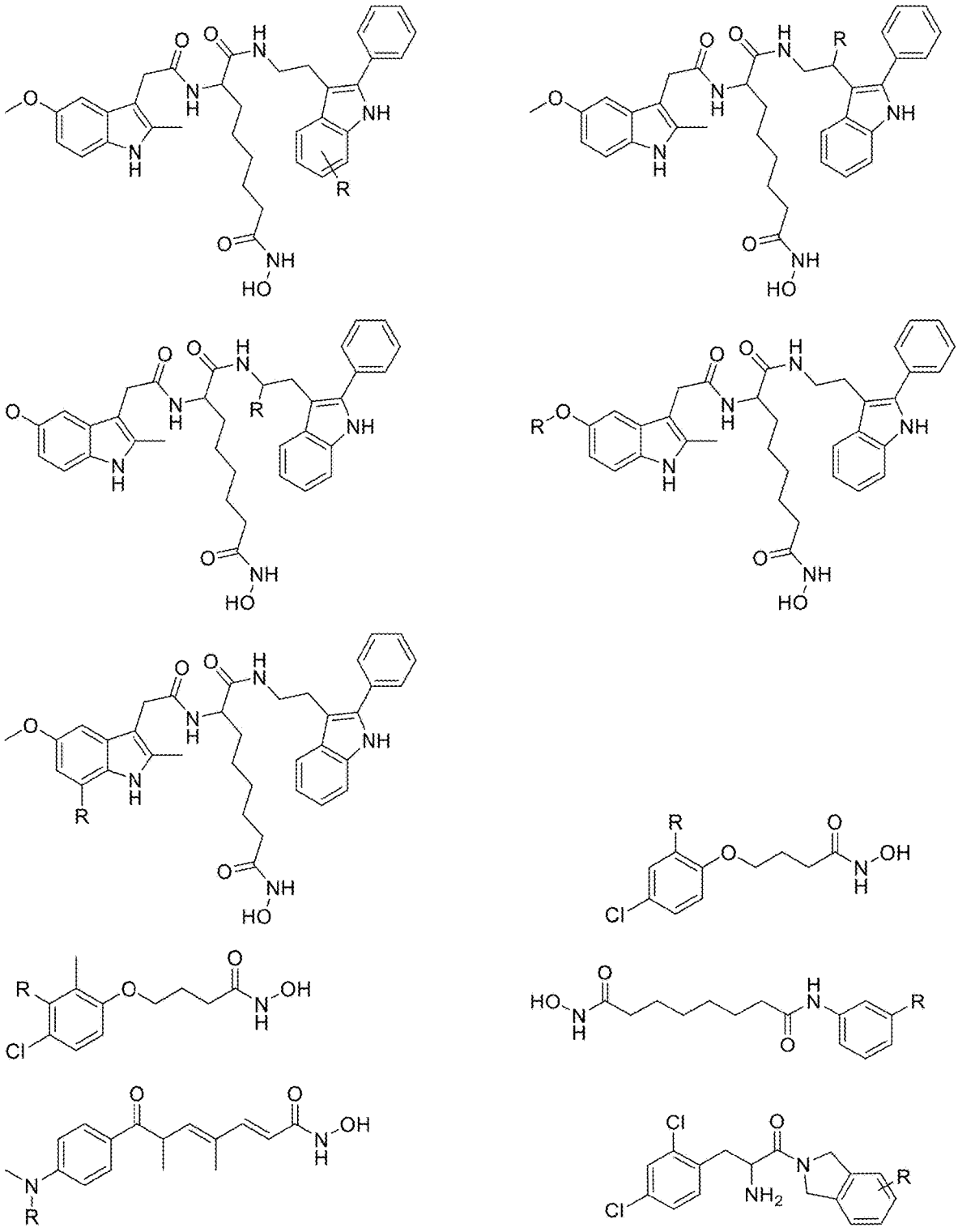

FIG. 3EEEEE

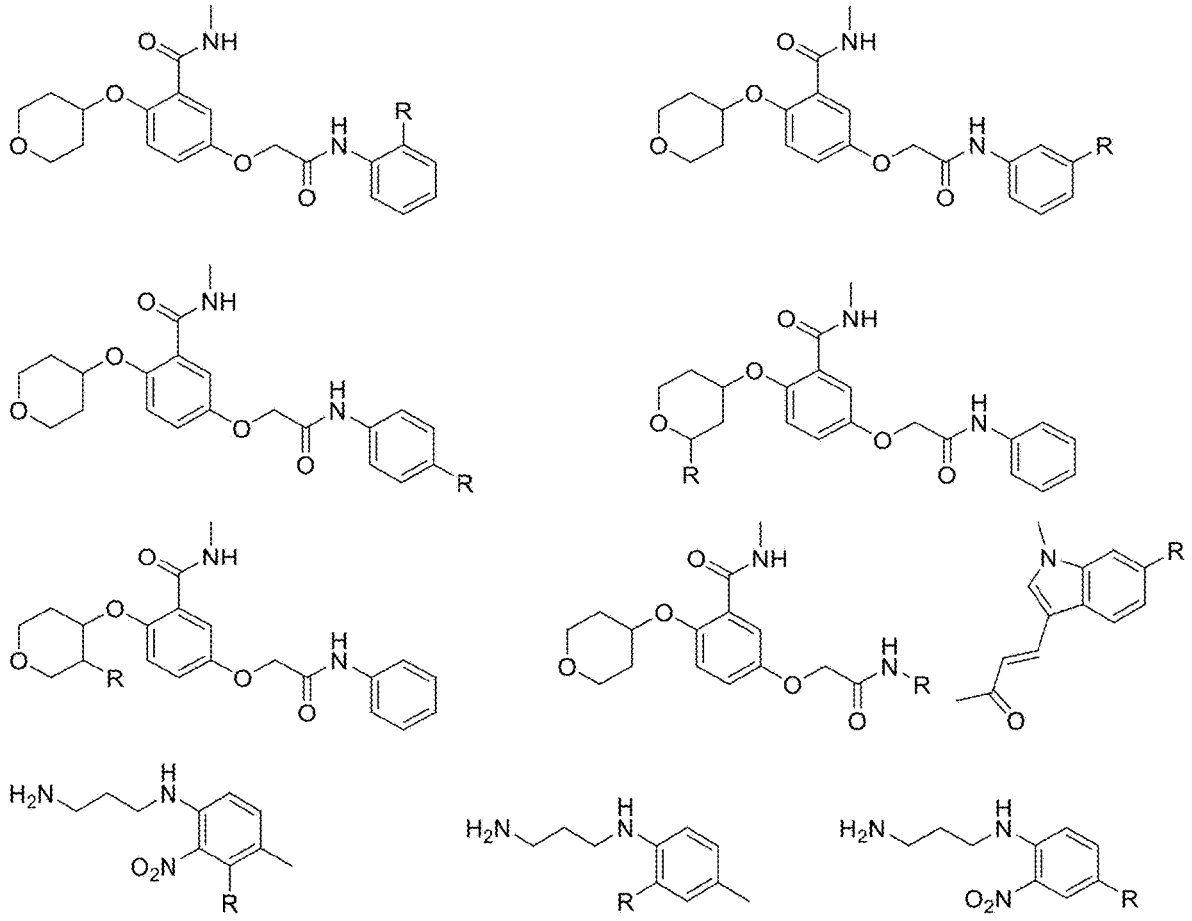

FIG. 3FFFFF

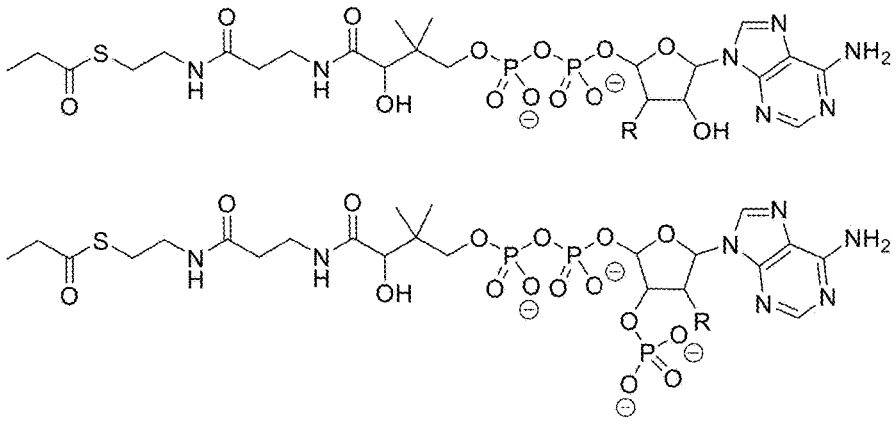

FIG. 3GGGGG

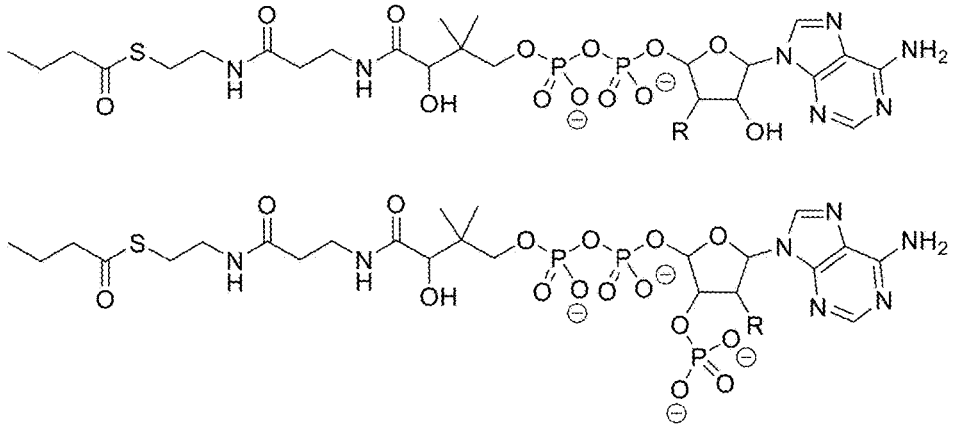

FIG. 3HHHHH

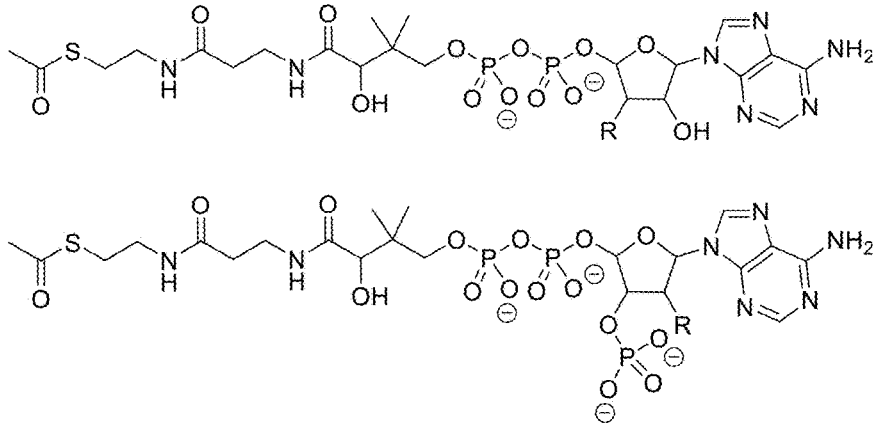

FIG. 3IIIII

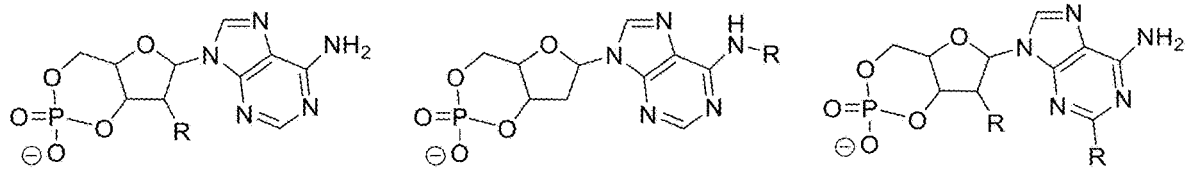

FIG. 3JJJJJ

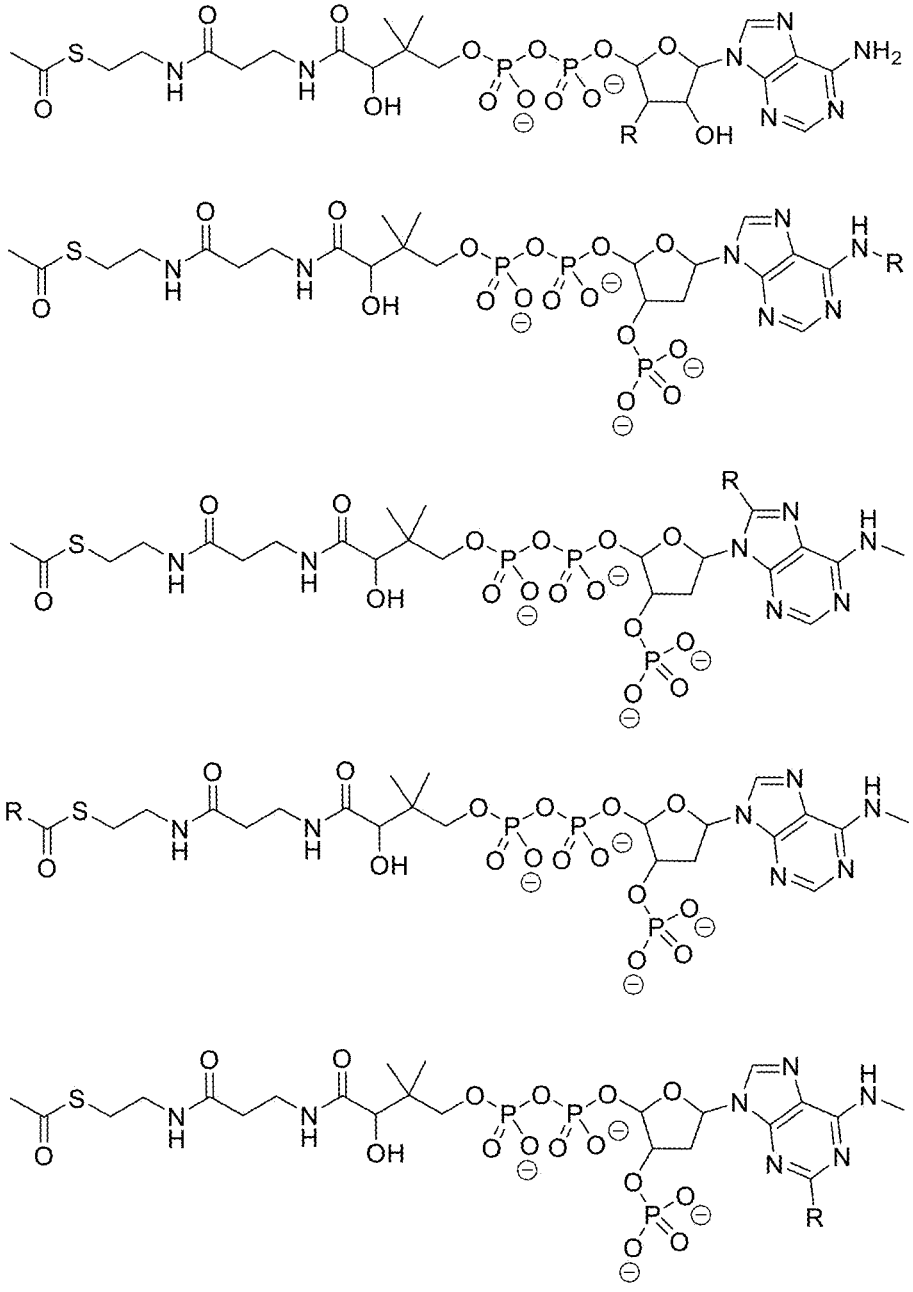

FIG. 3KKKKK

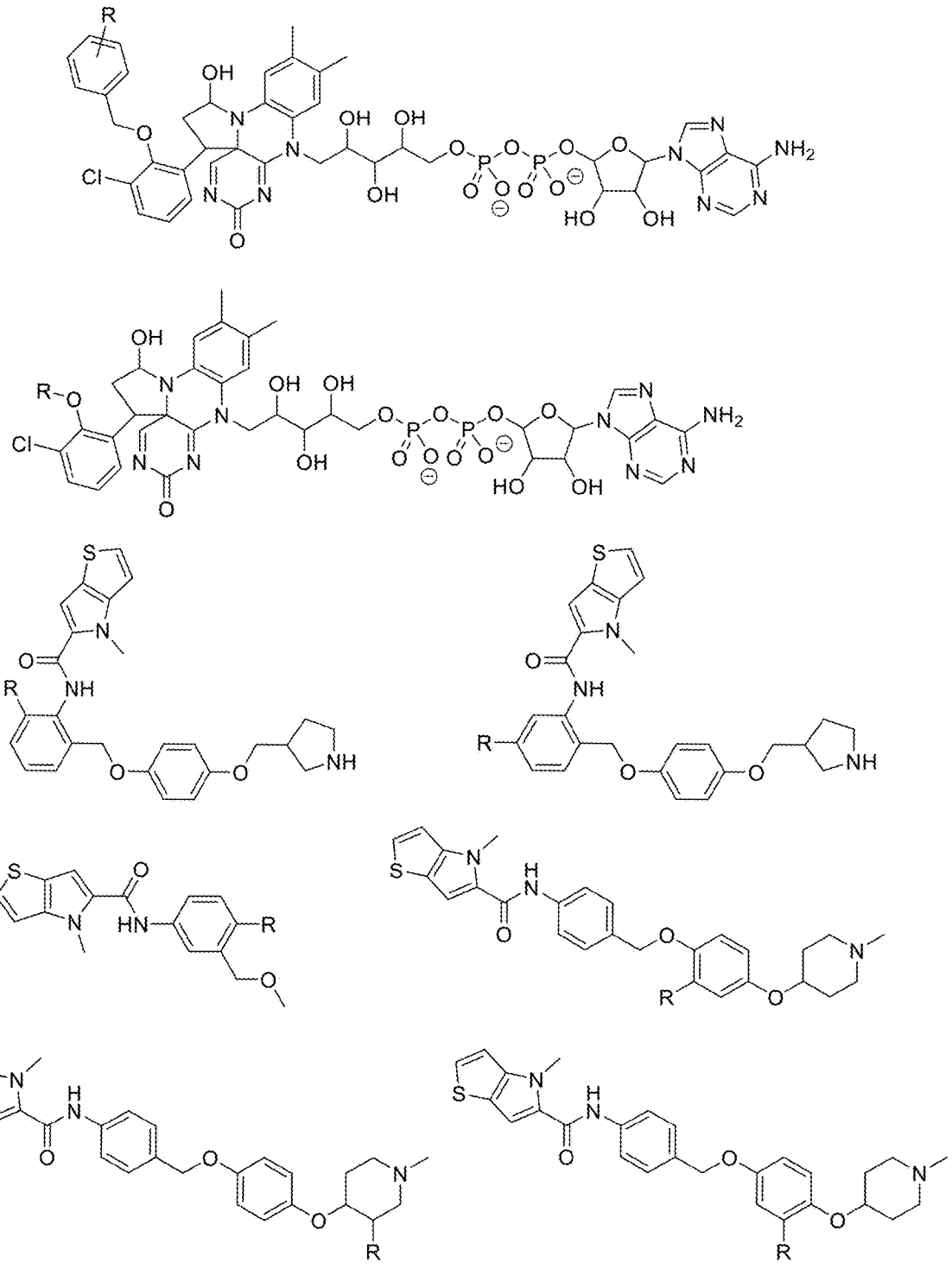

FIG. 3LLLLL

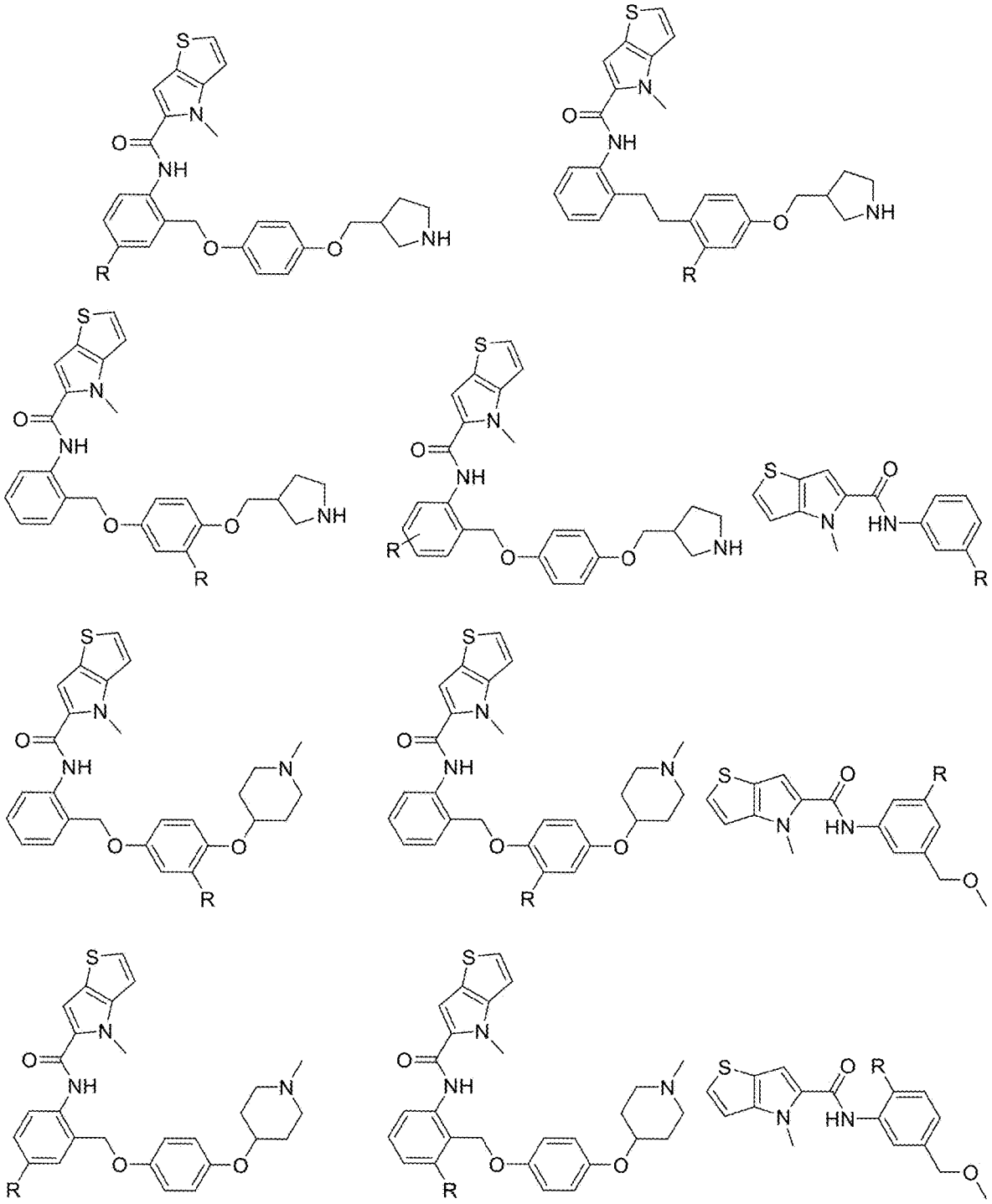
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FIG. 3MMMMM

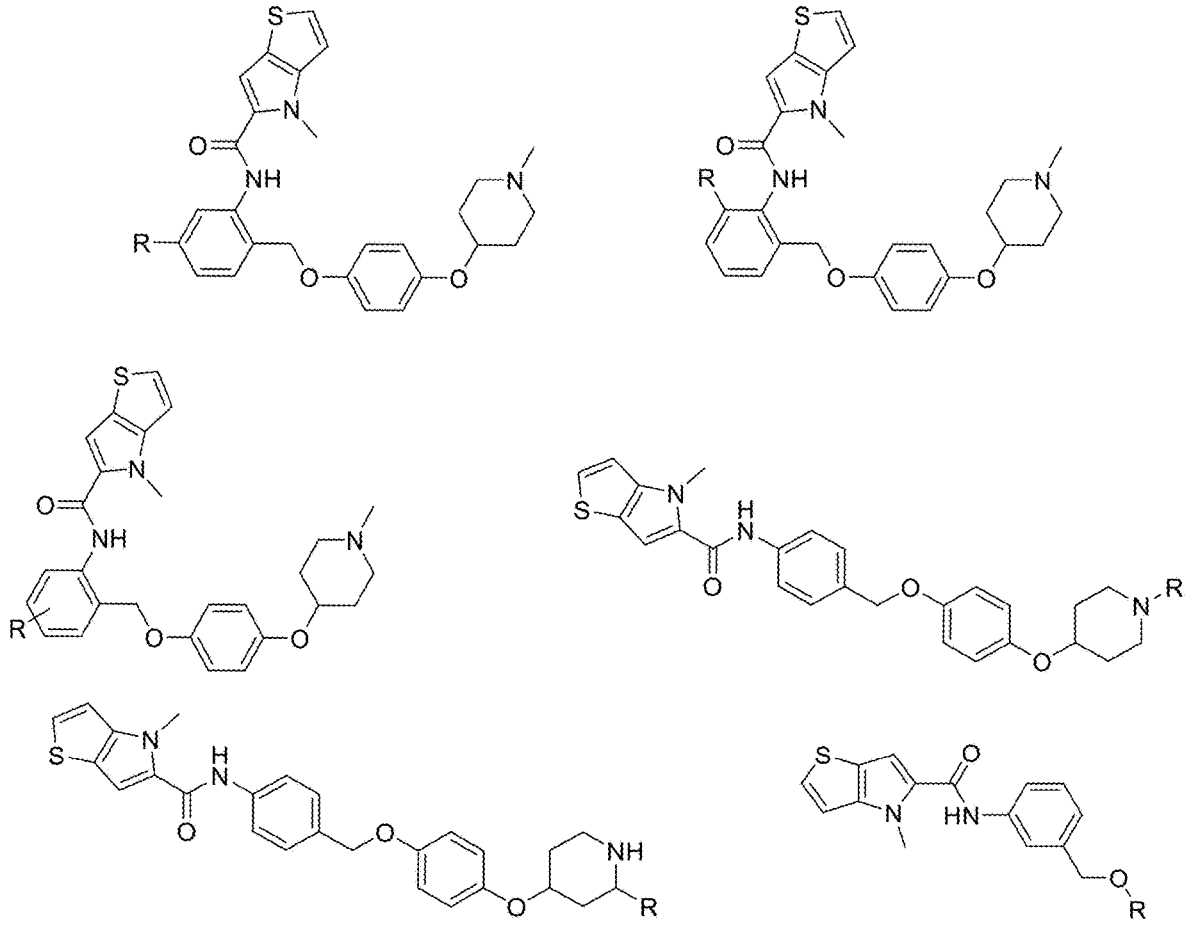

FIG. 3NNNNN

FIG. 3OOOOO

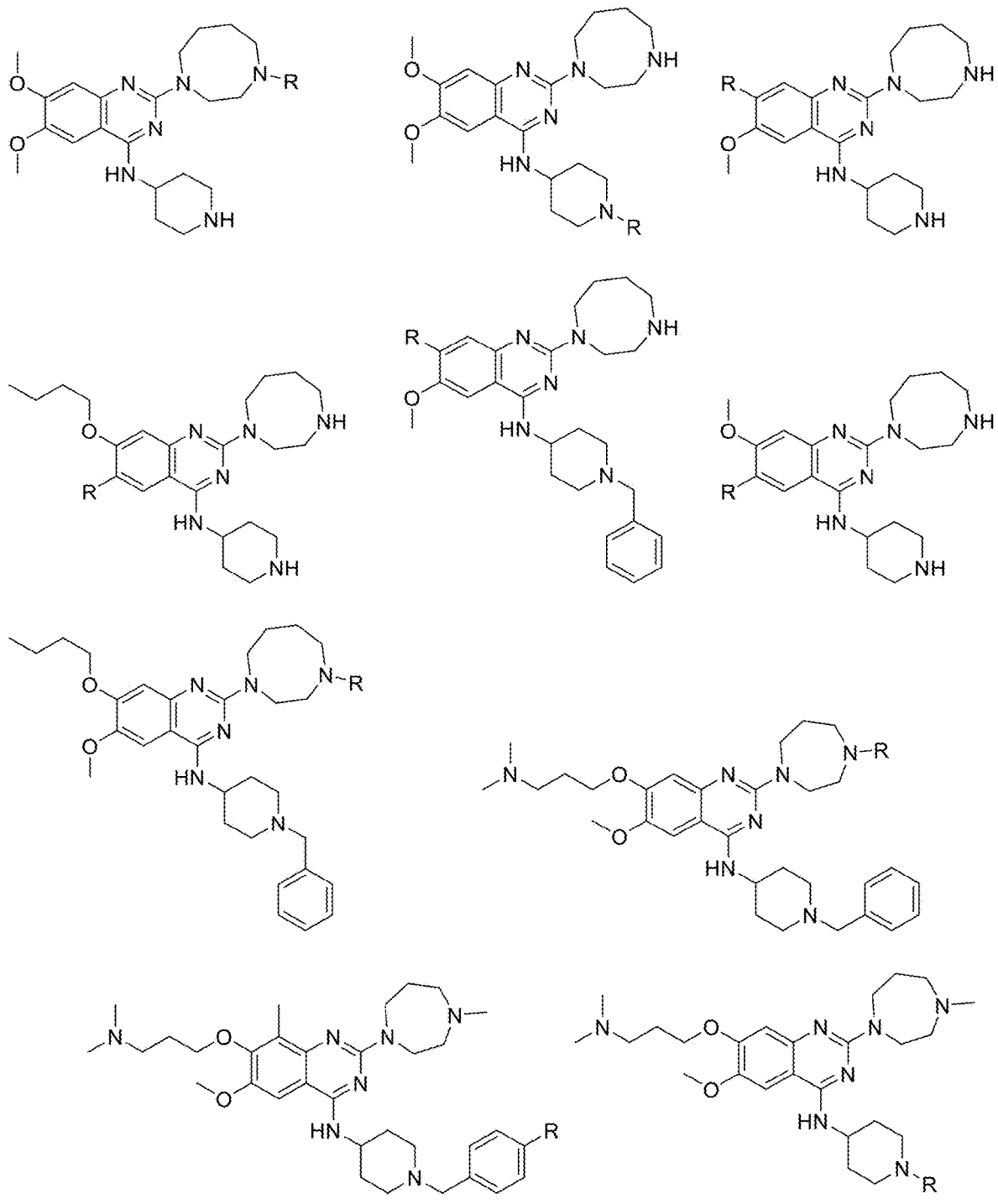

FIG. 3PPPPP

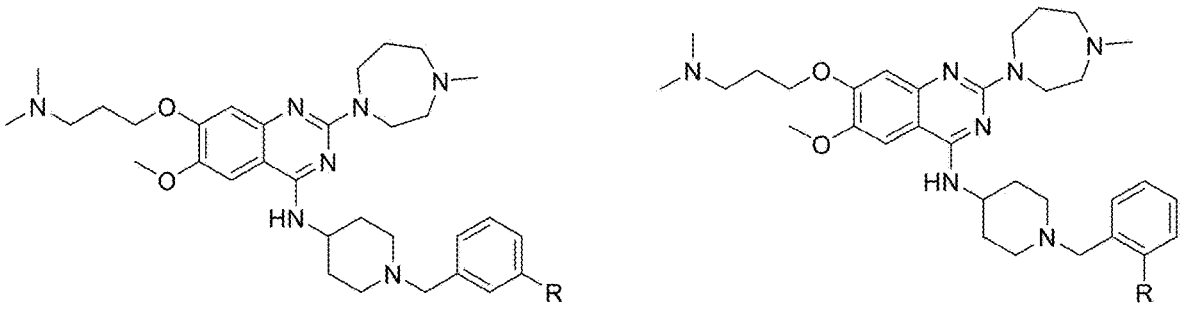

FIG. 3QQQQQ

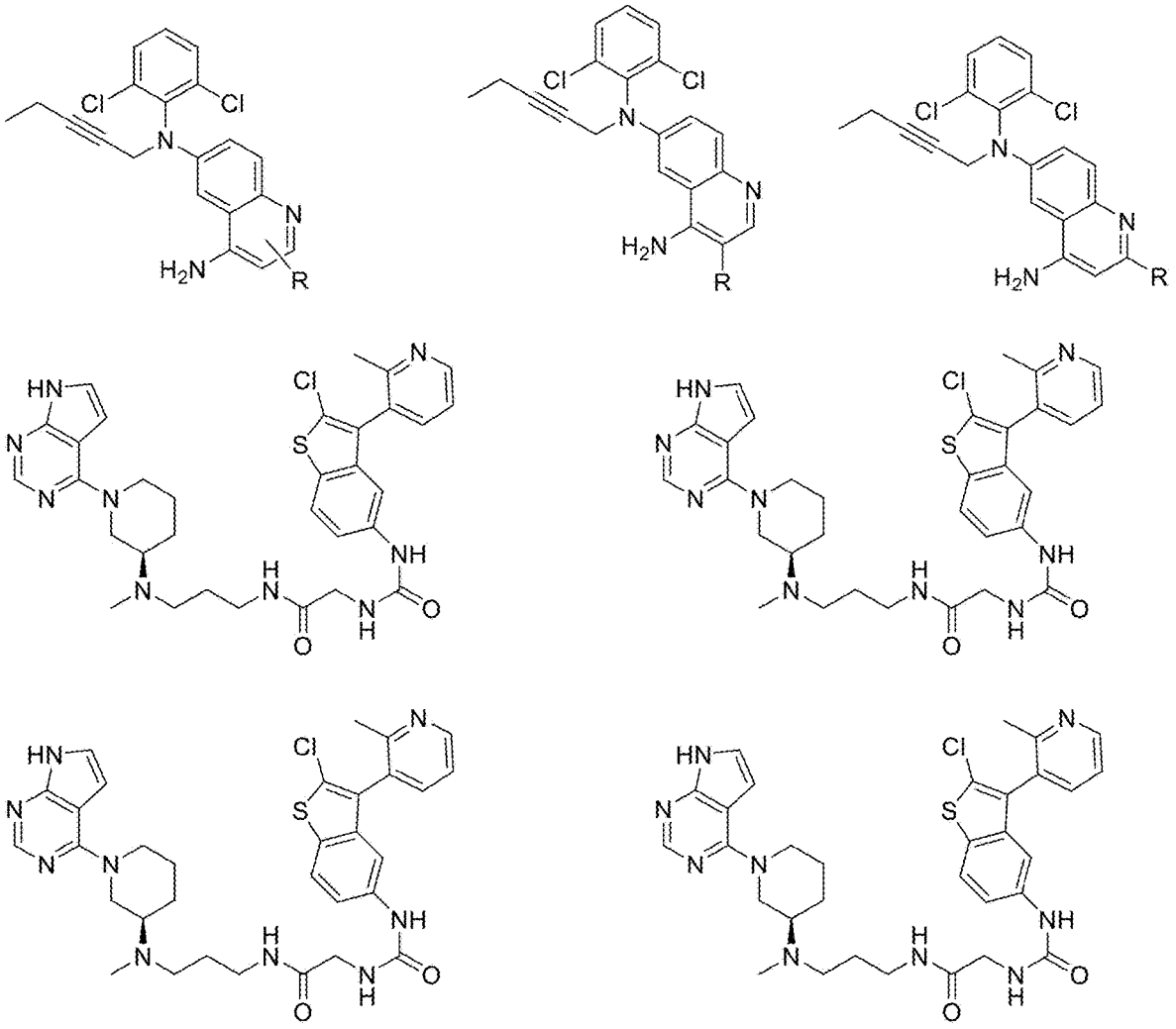

FIG. 3RRRRR

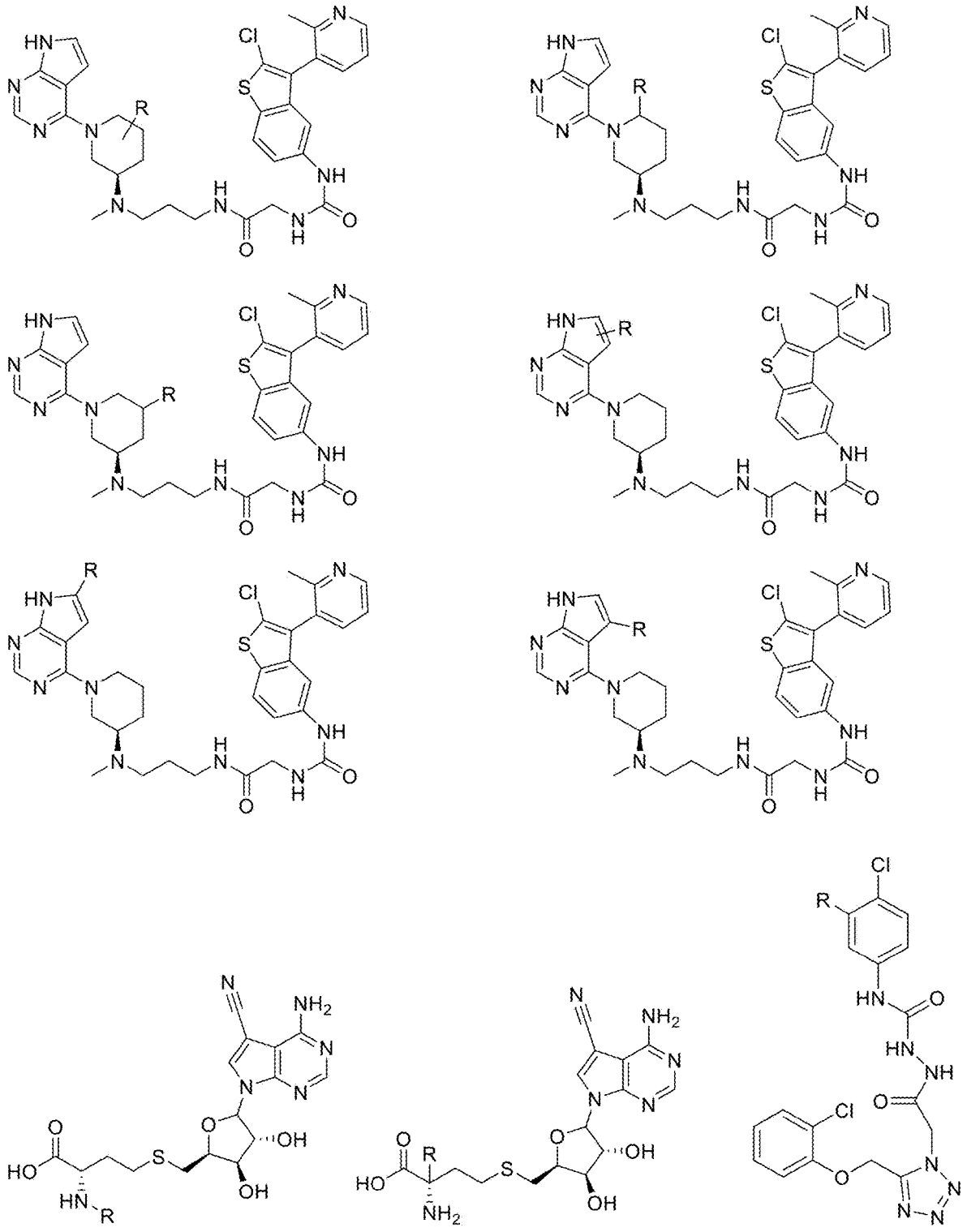

FIG. 3SSSSS

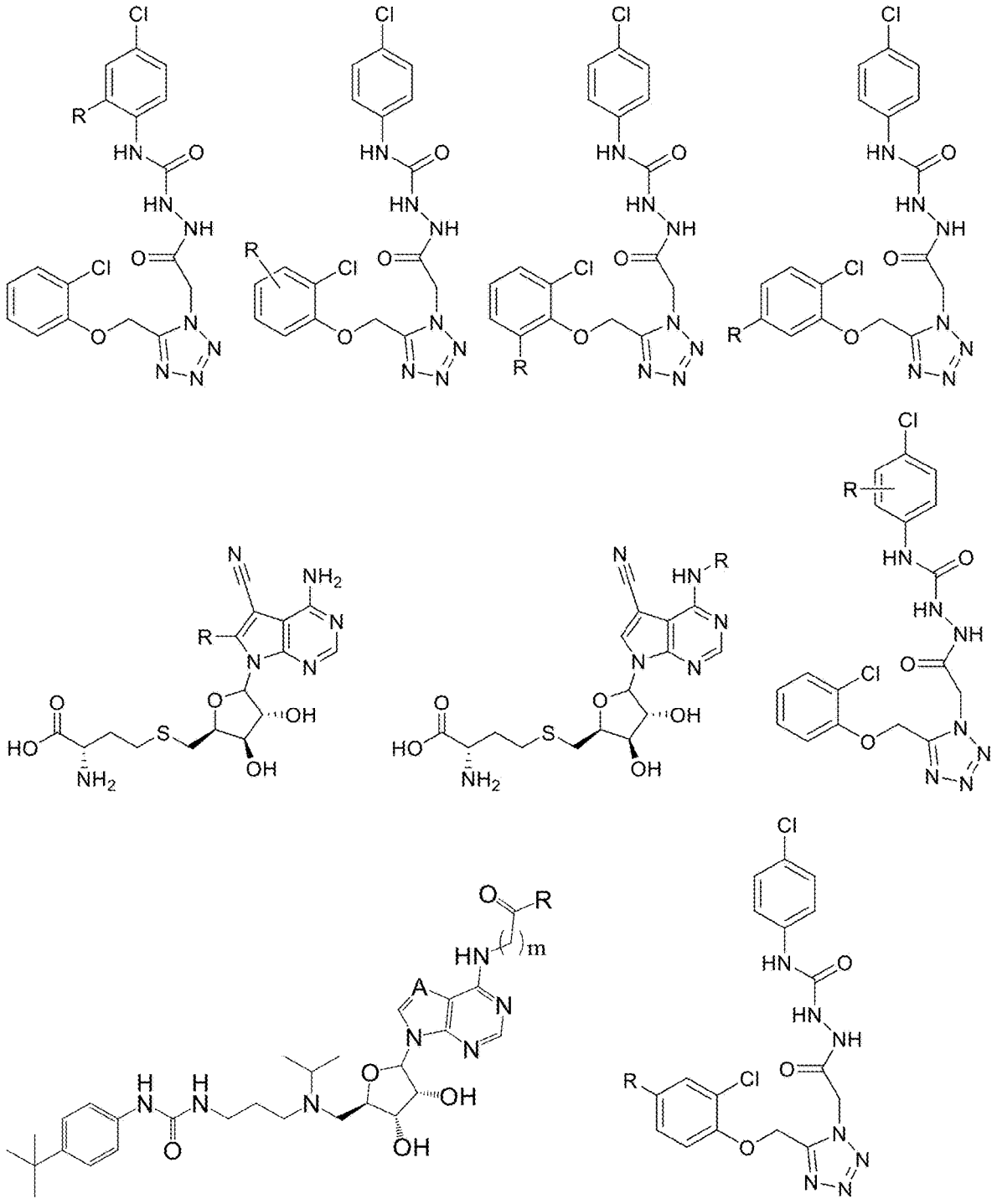

FIG. 3TTTTT

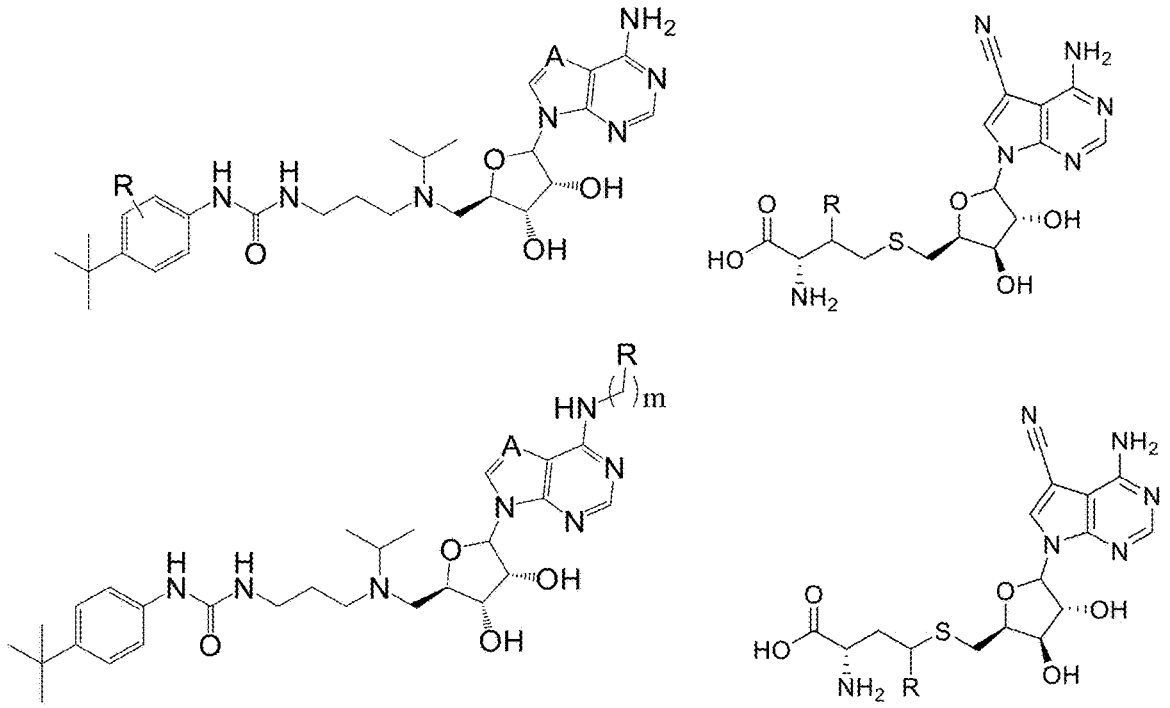

FIG. 3UUUUU

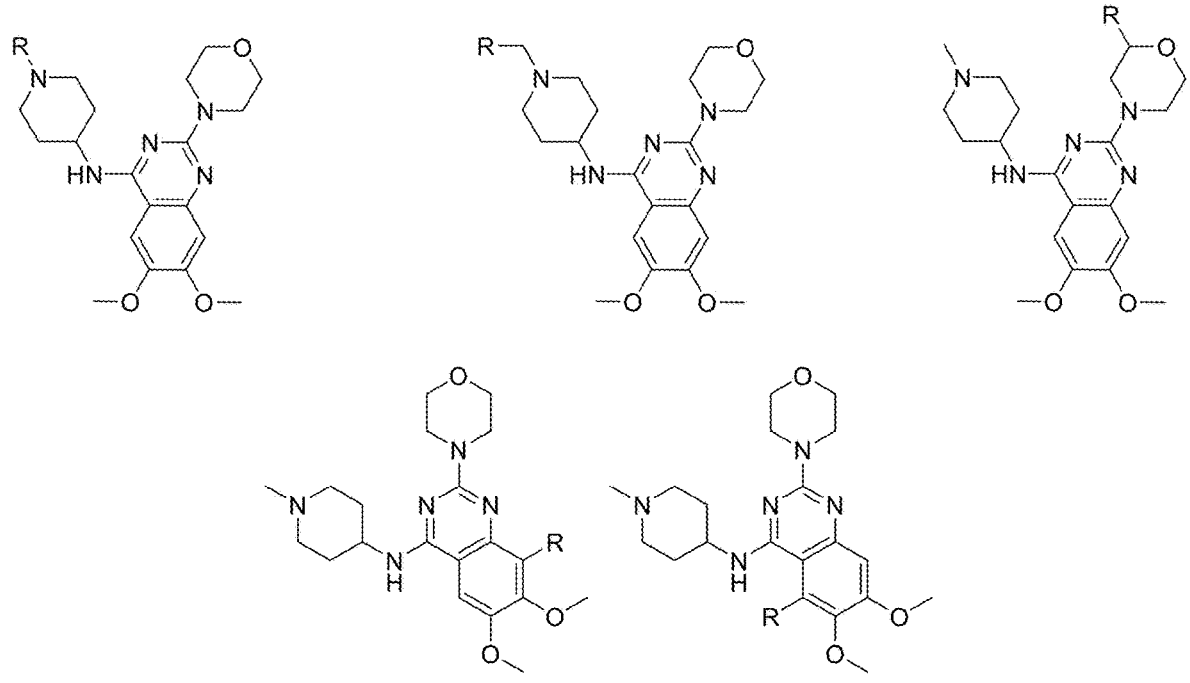

FIG. 3VVVVV

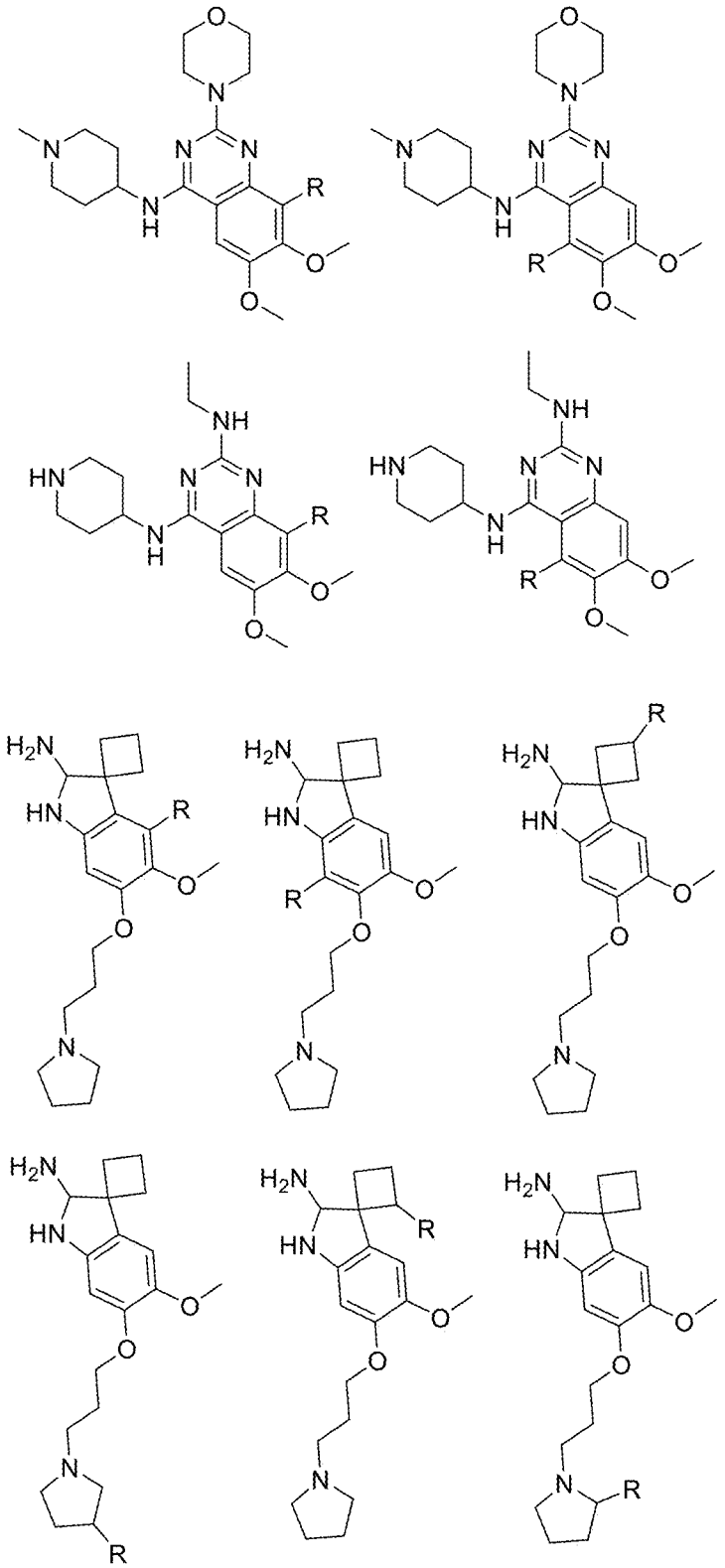

FIG. 3WWWWW

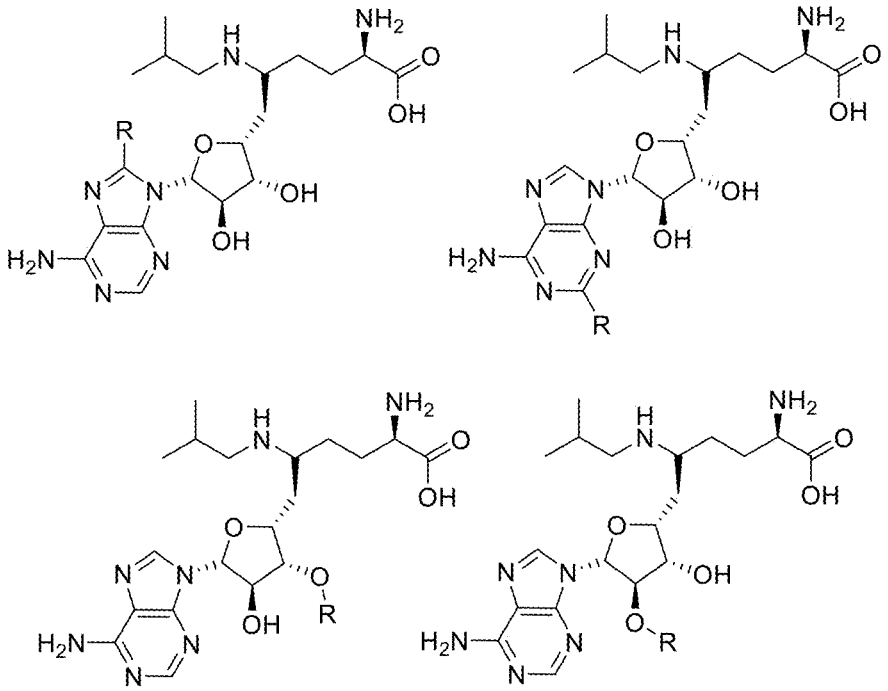

FIG. 3XXXXX

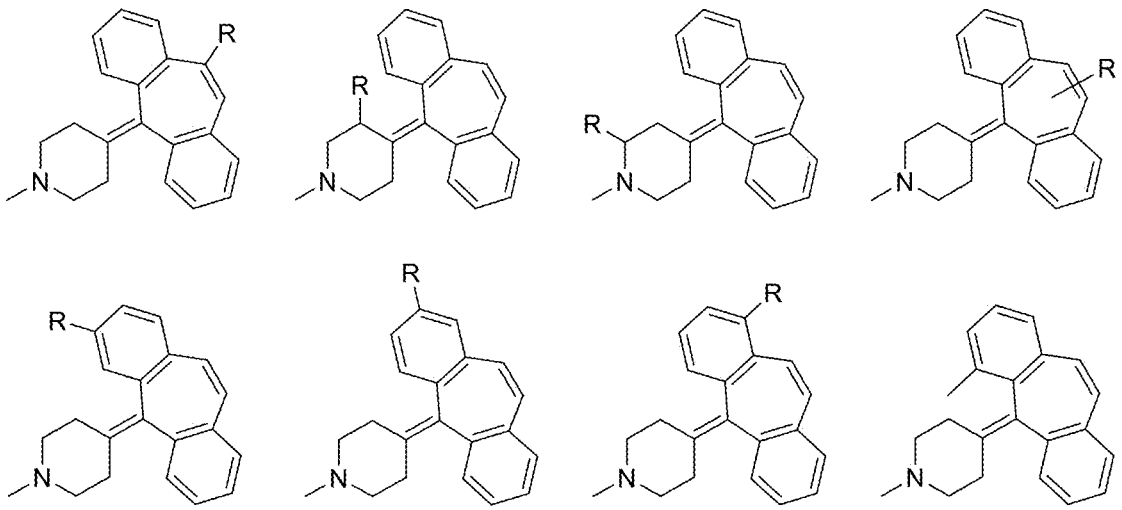

FIG. 3YYYYY

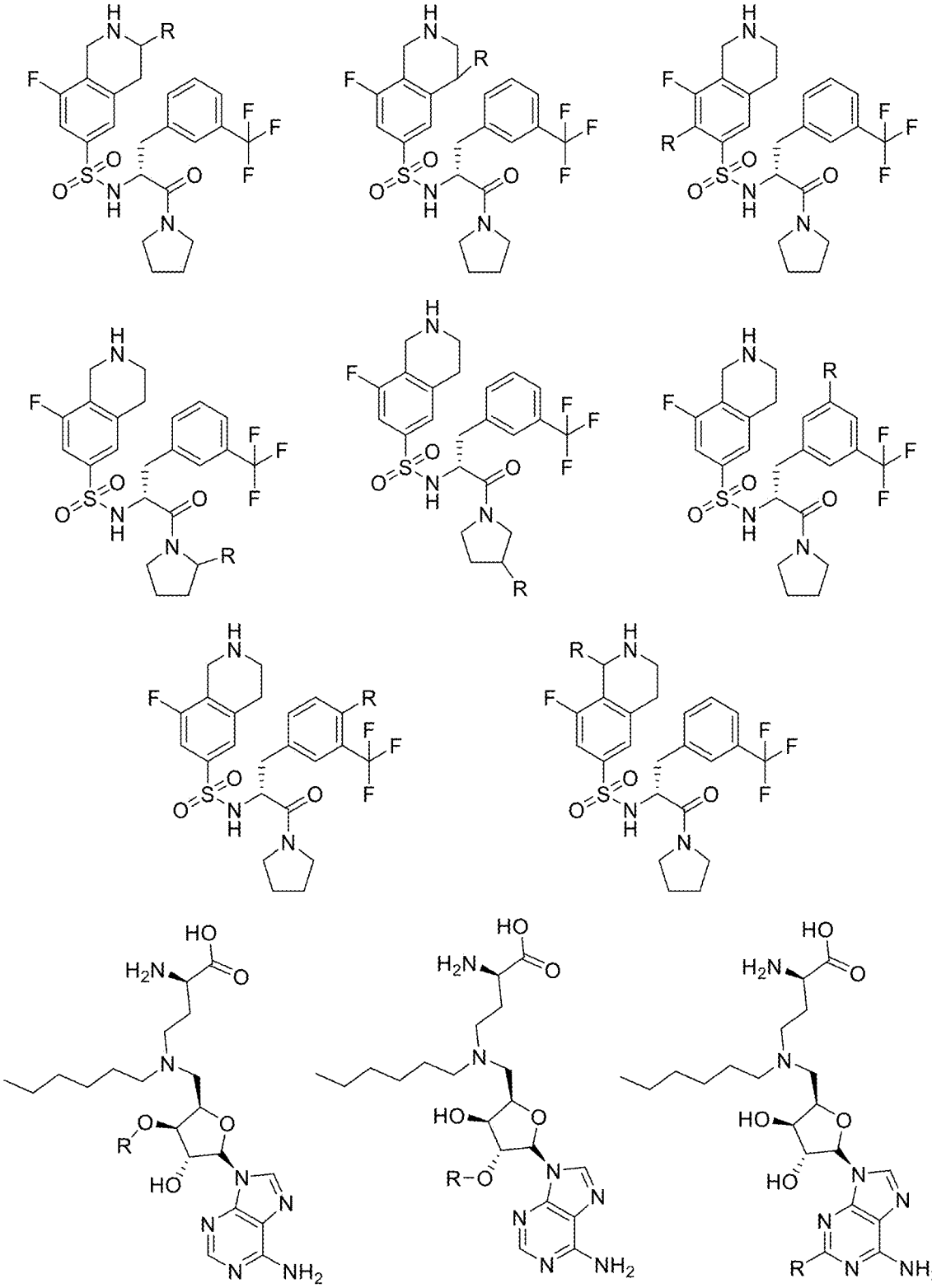

FIG. 3ZZZZZ

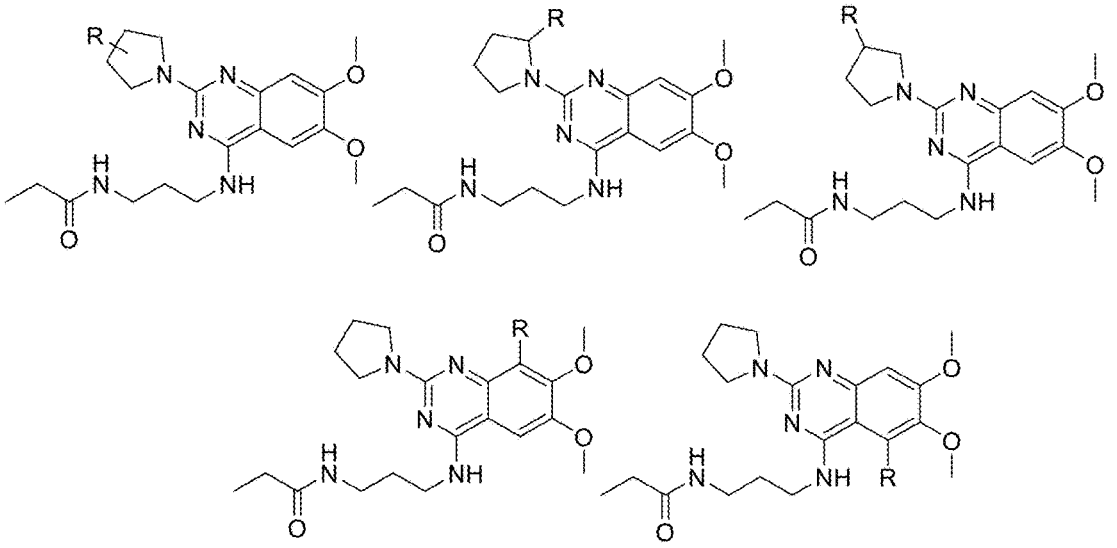

FIG. 4A

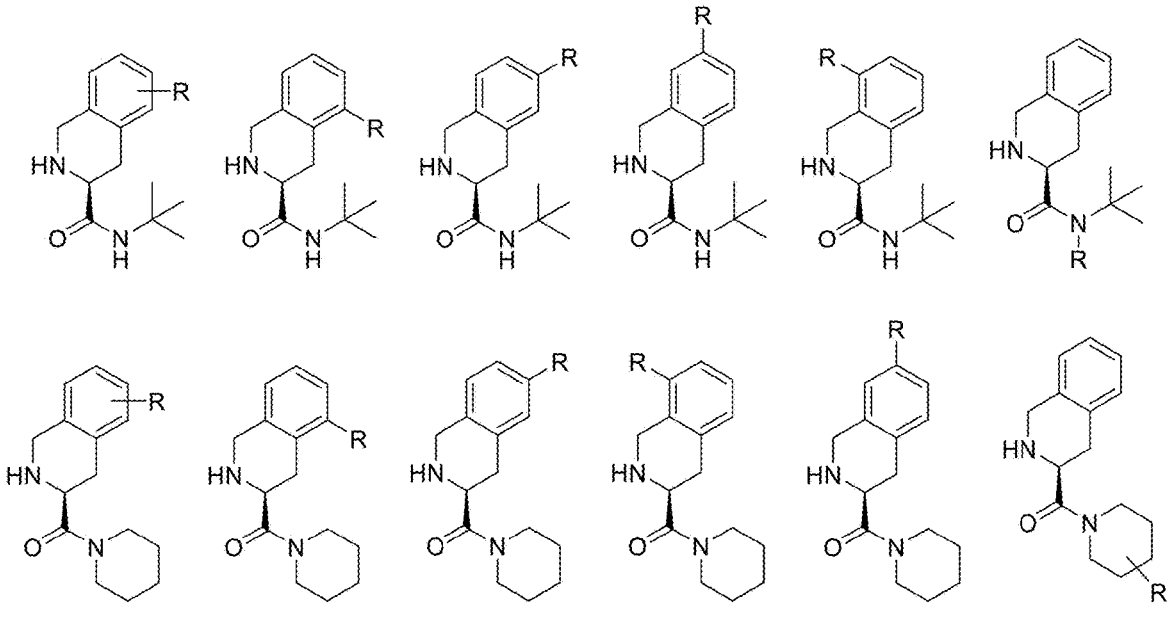

FIG. 4B

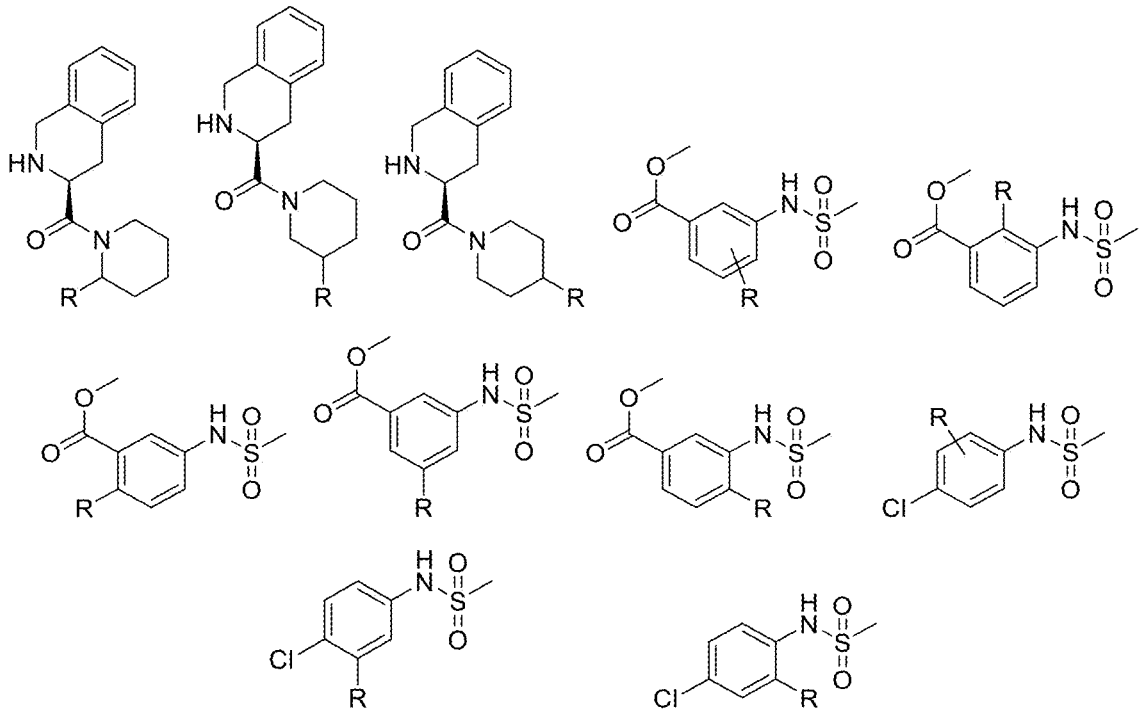

FIG. 4C

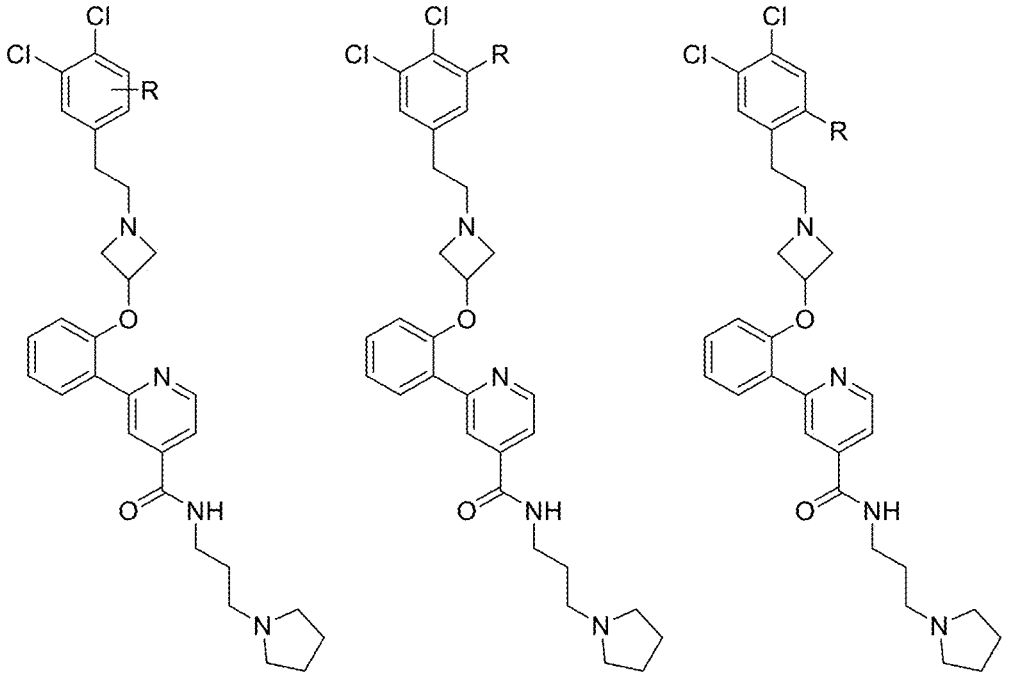

FIG. 4D

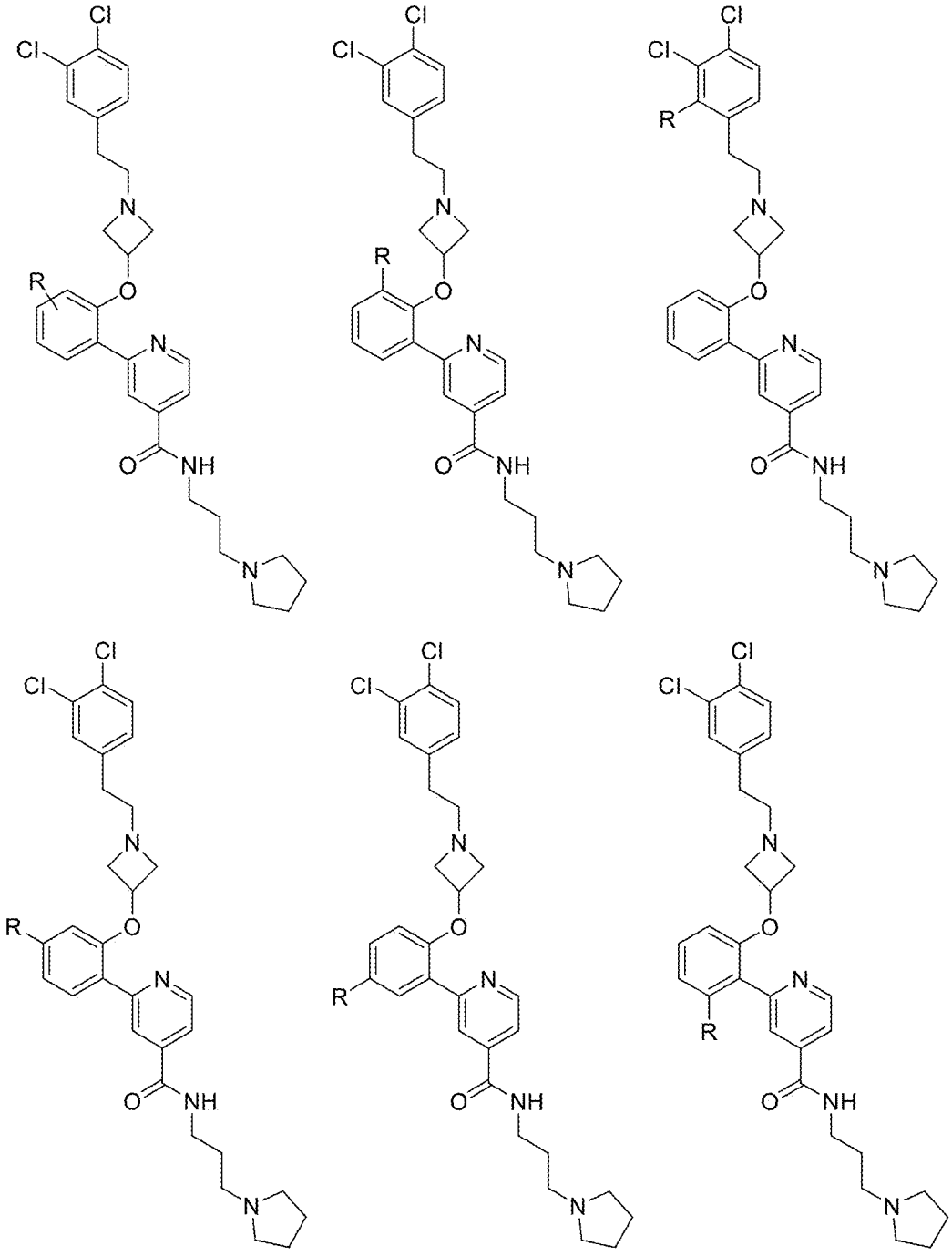

FIG. 4E

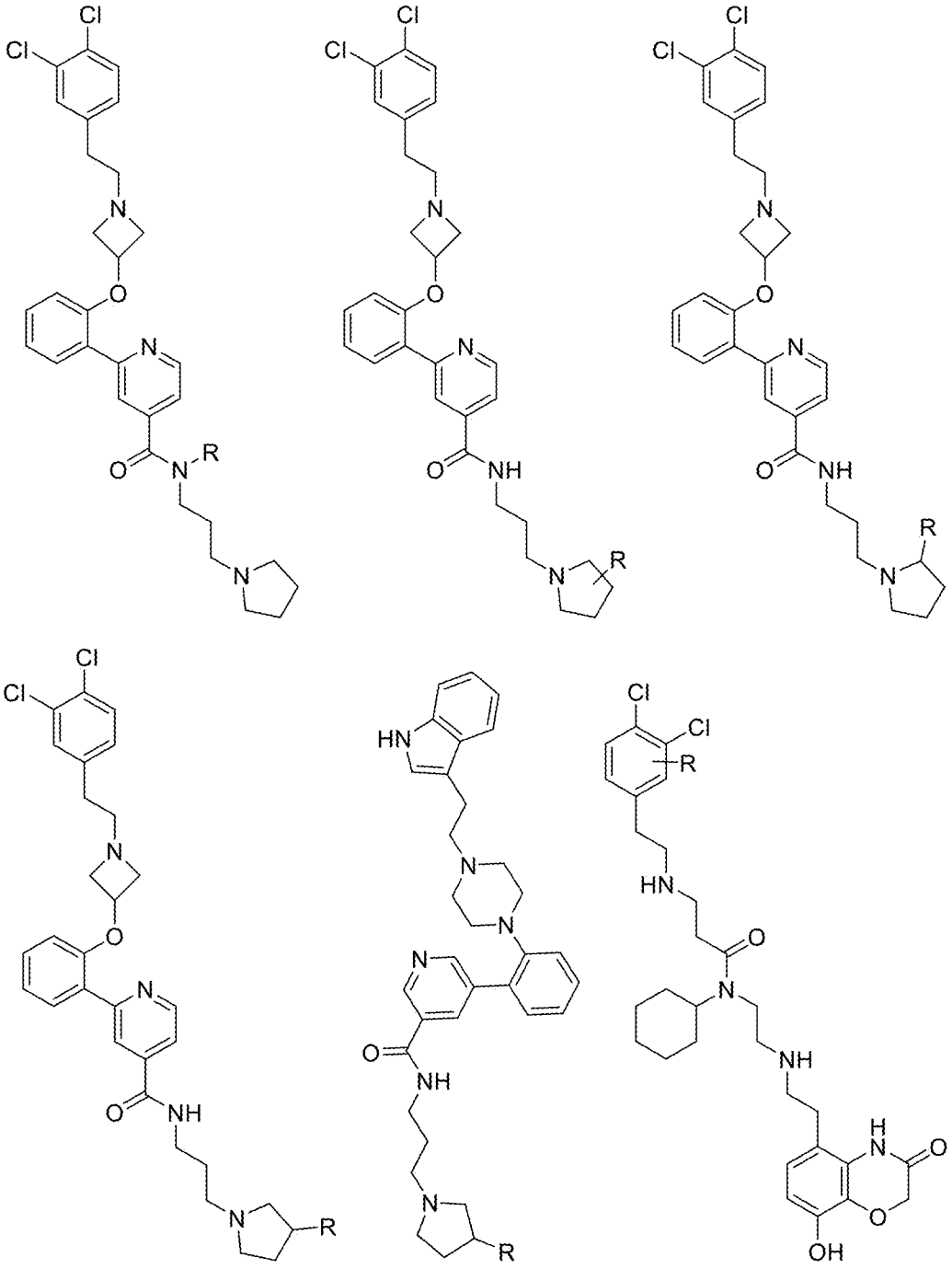

FIG. 4F

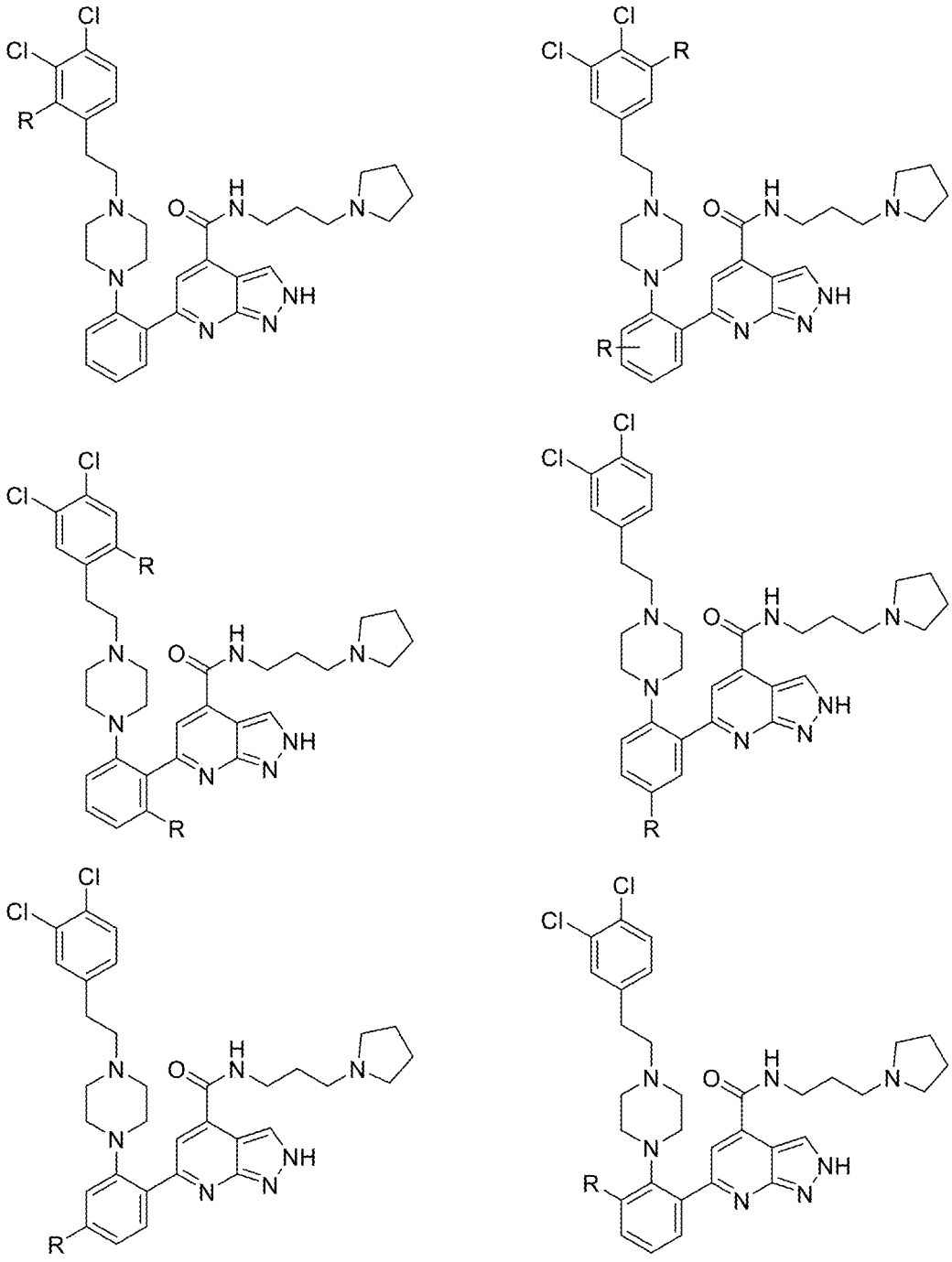

FIG. 4G

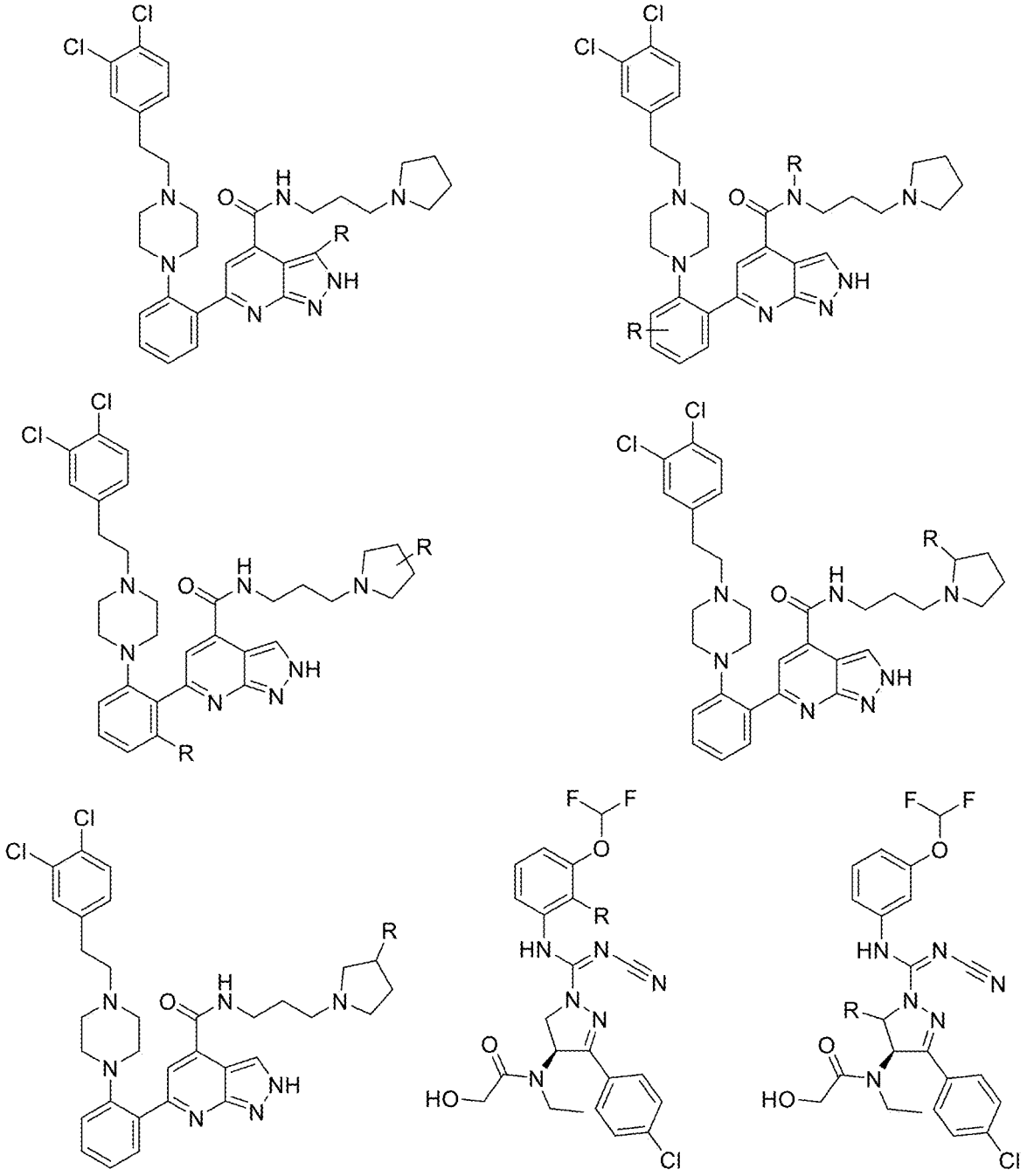

FIG. 4H

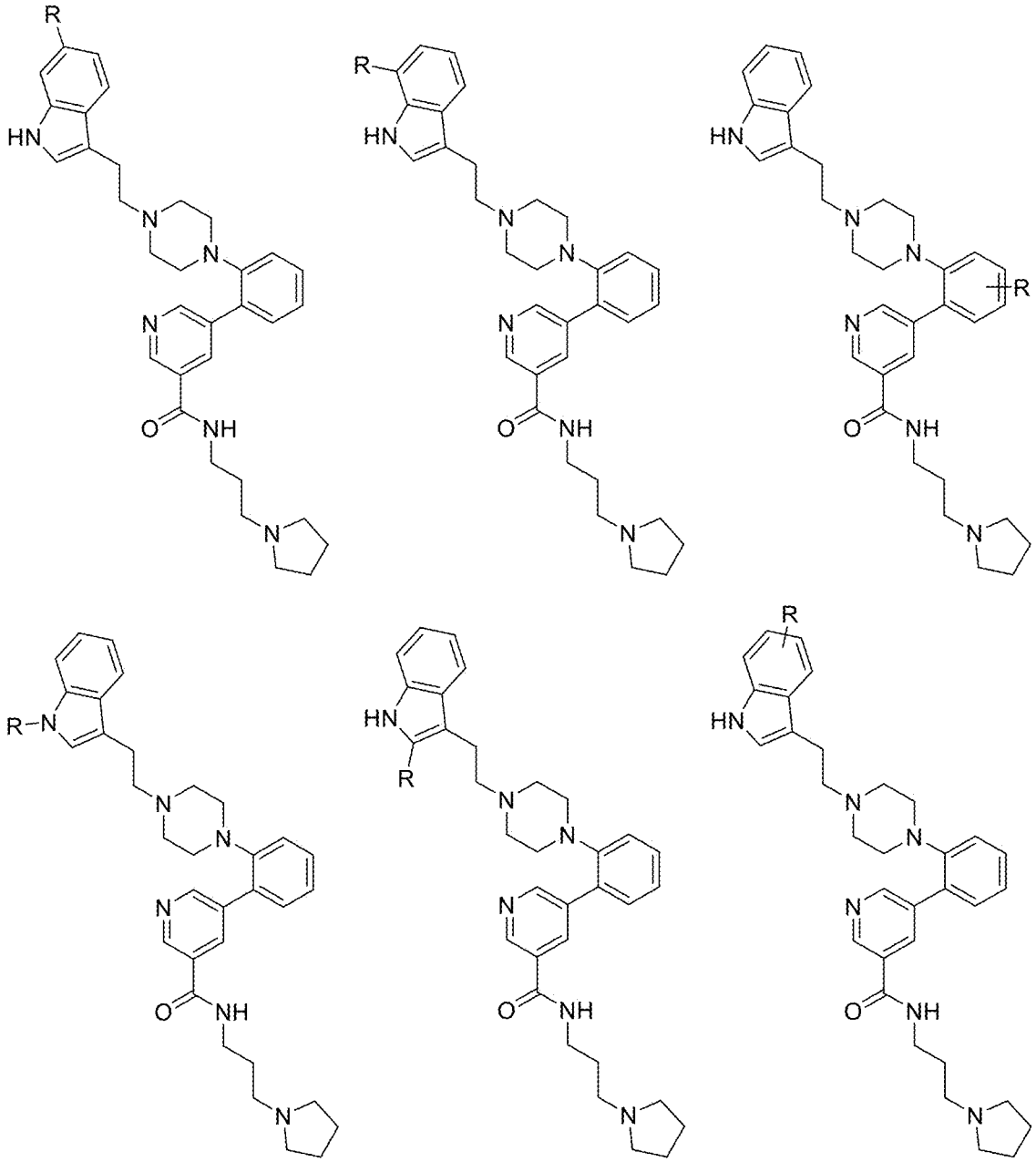

FIG. 4I

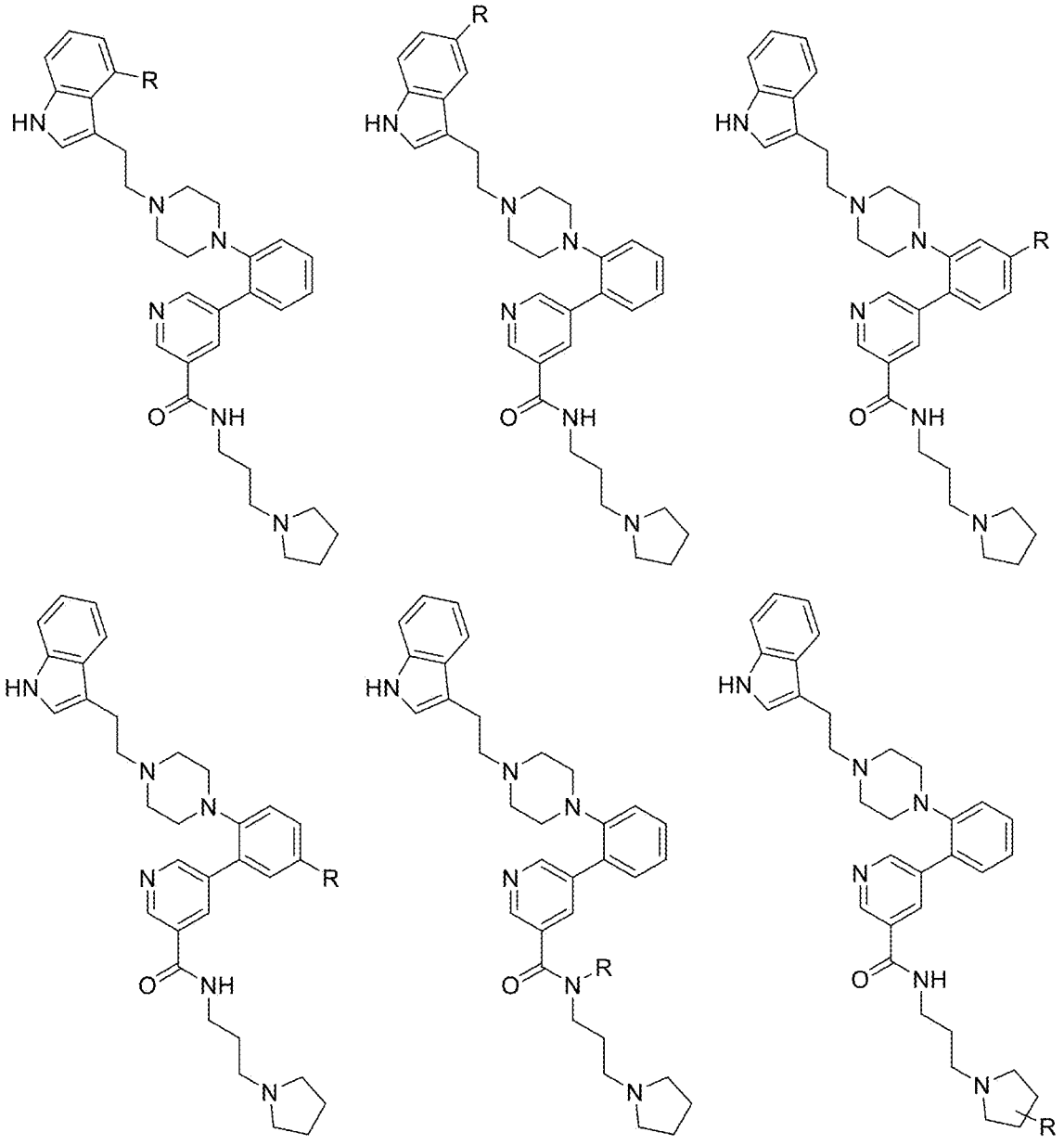
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FIG. 4J

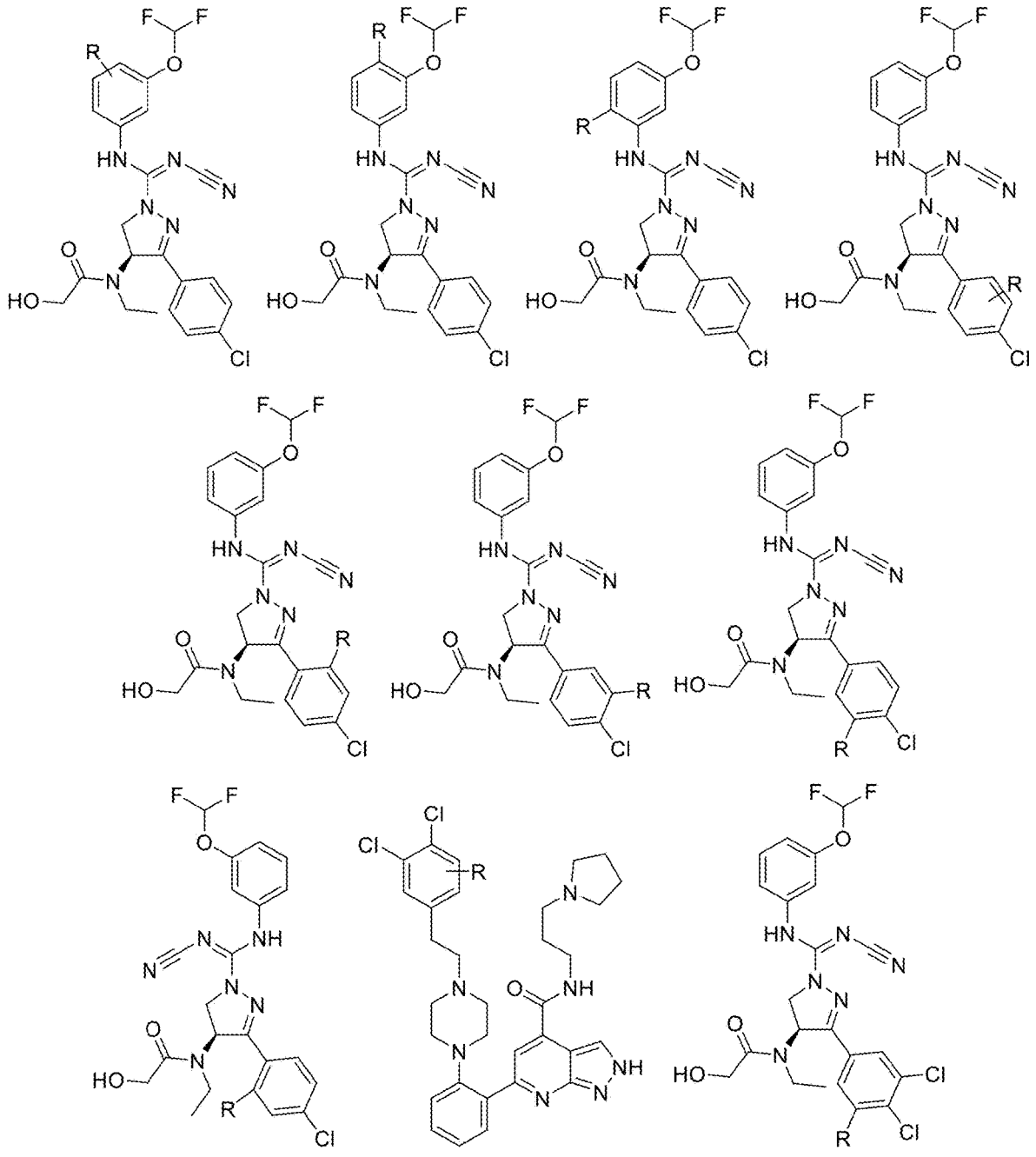

FIG. 4K

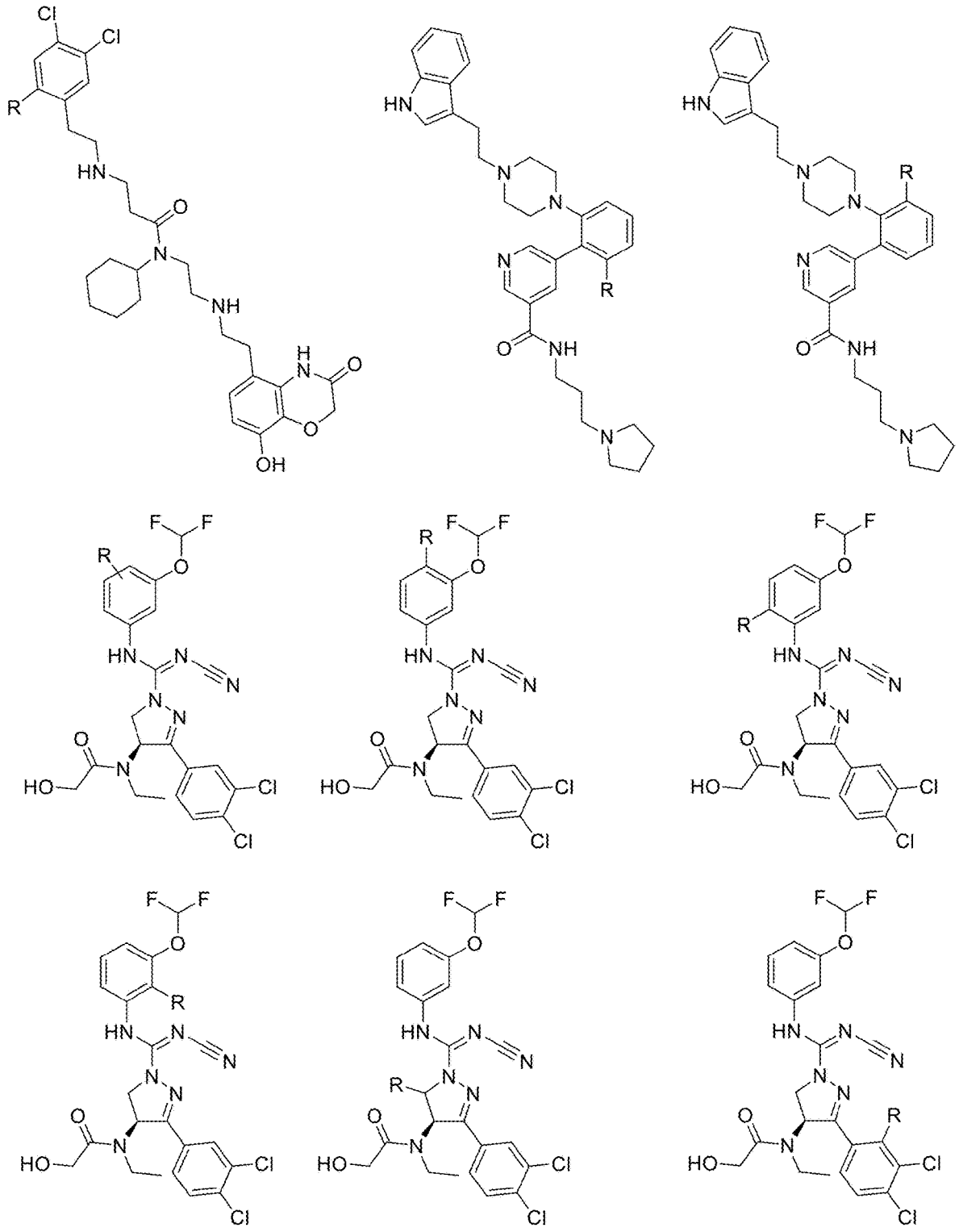

FIG. 4L

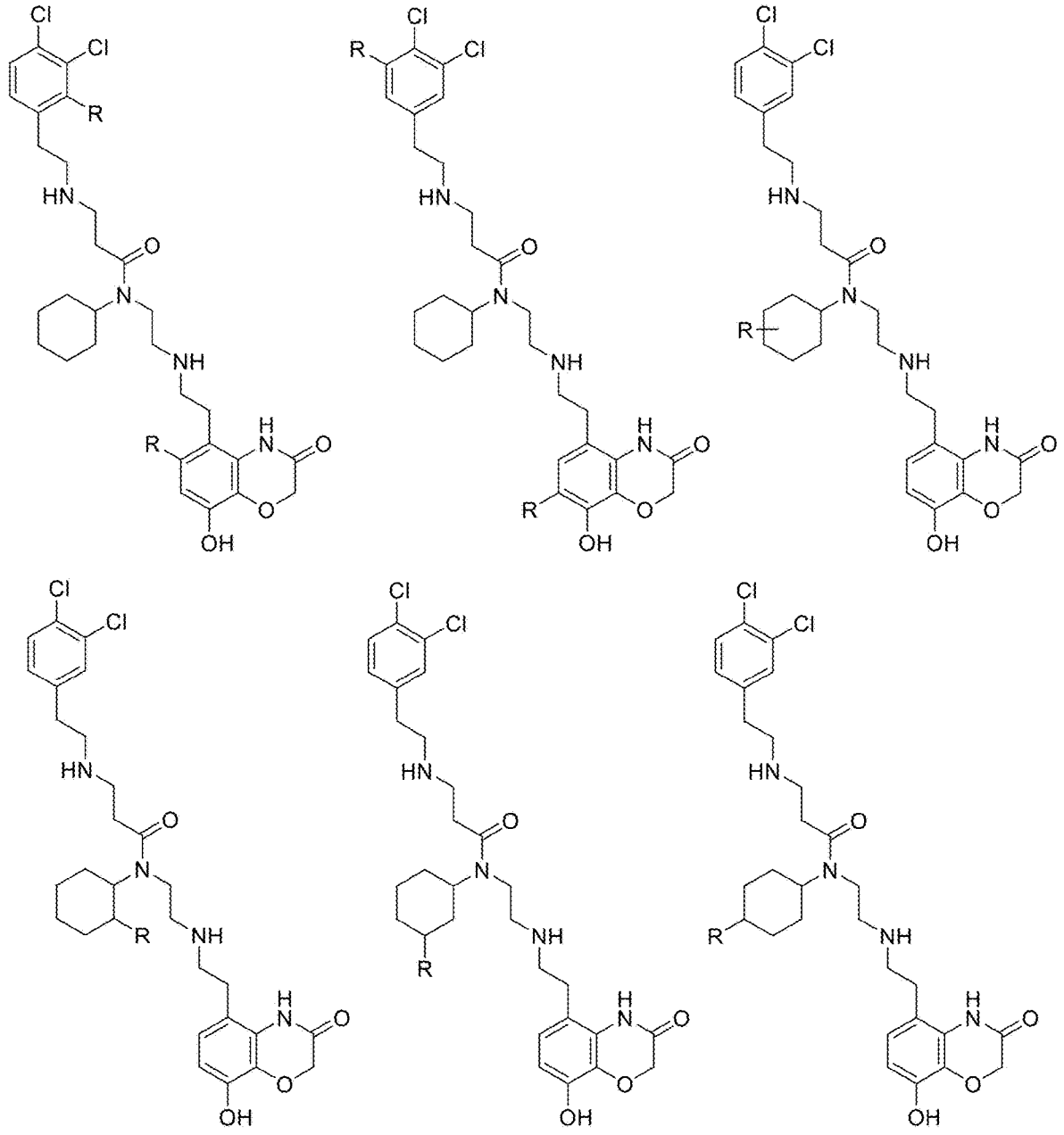

FIG. 4M

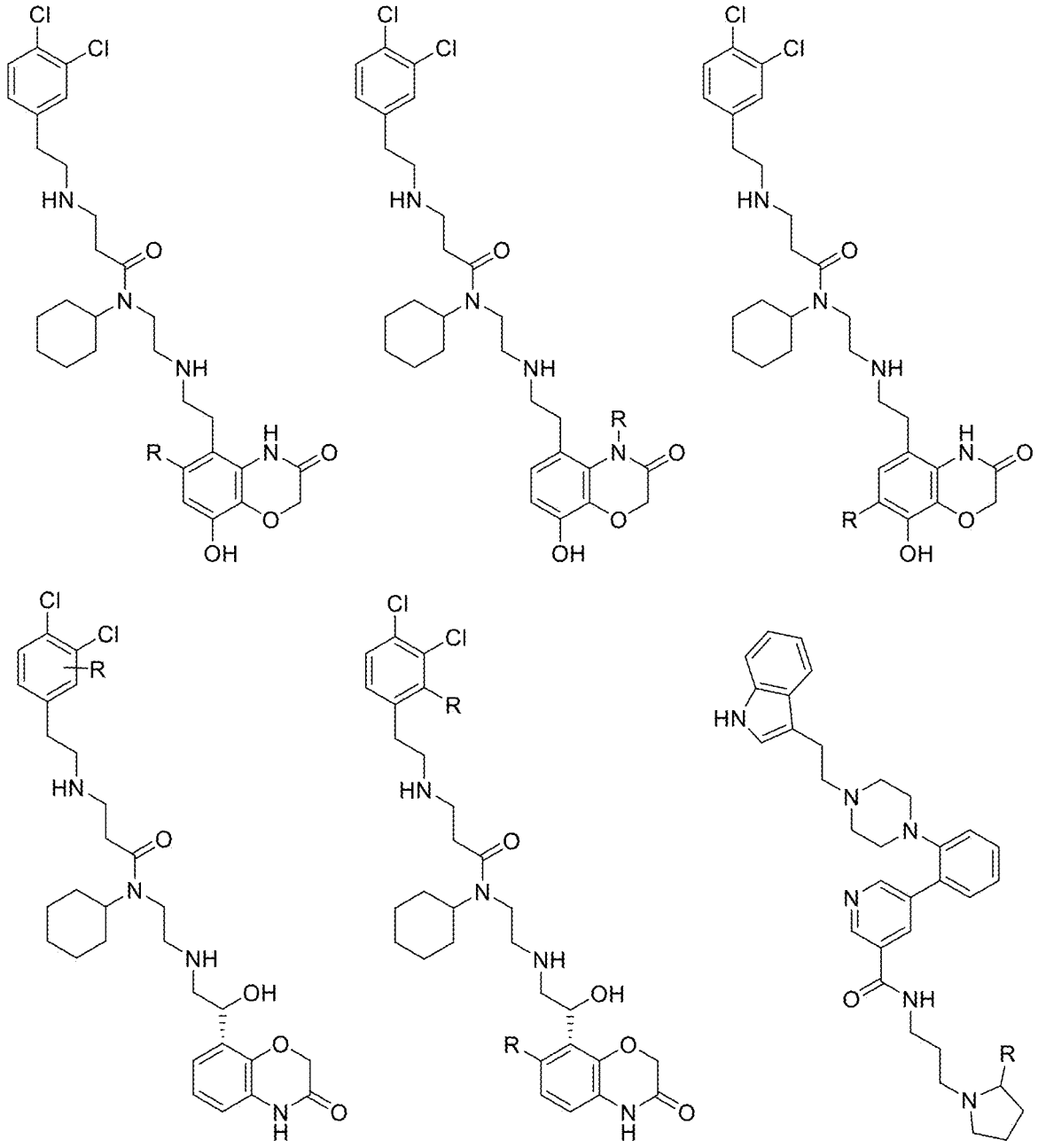
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FIG. 4N

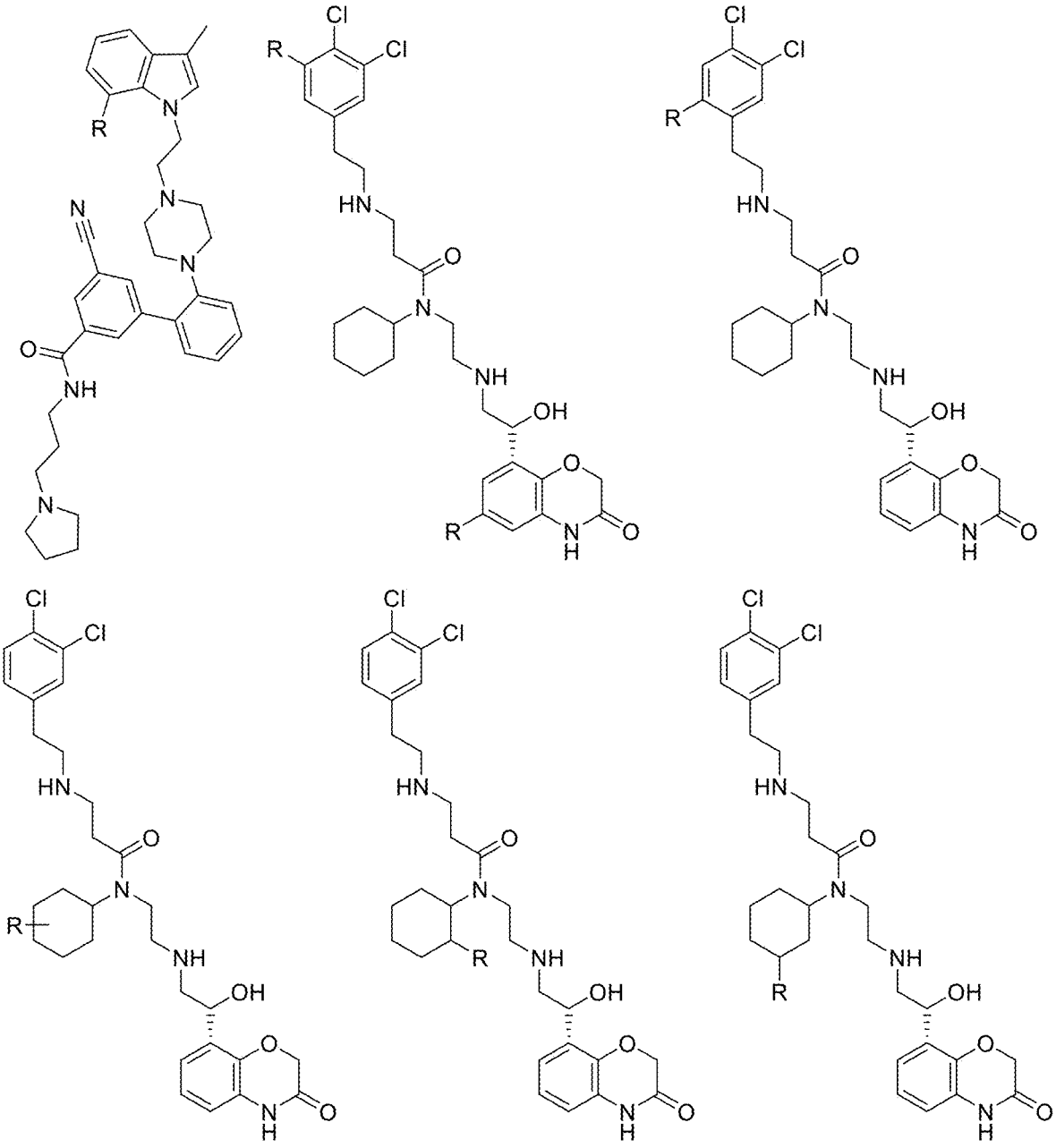


FIG. 4O

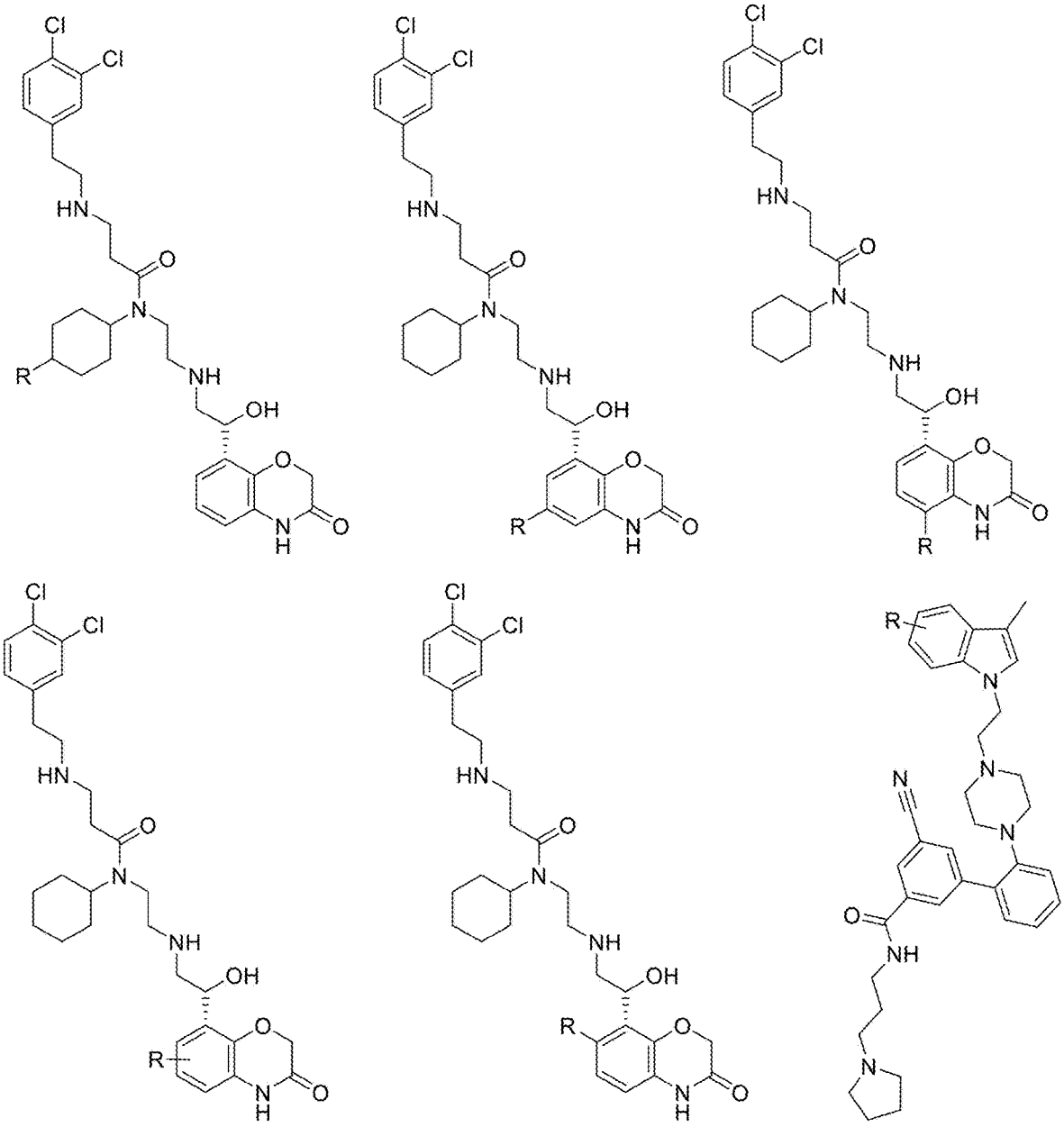


FIG. 4P

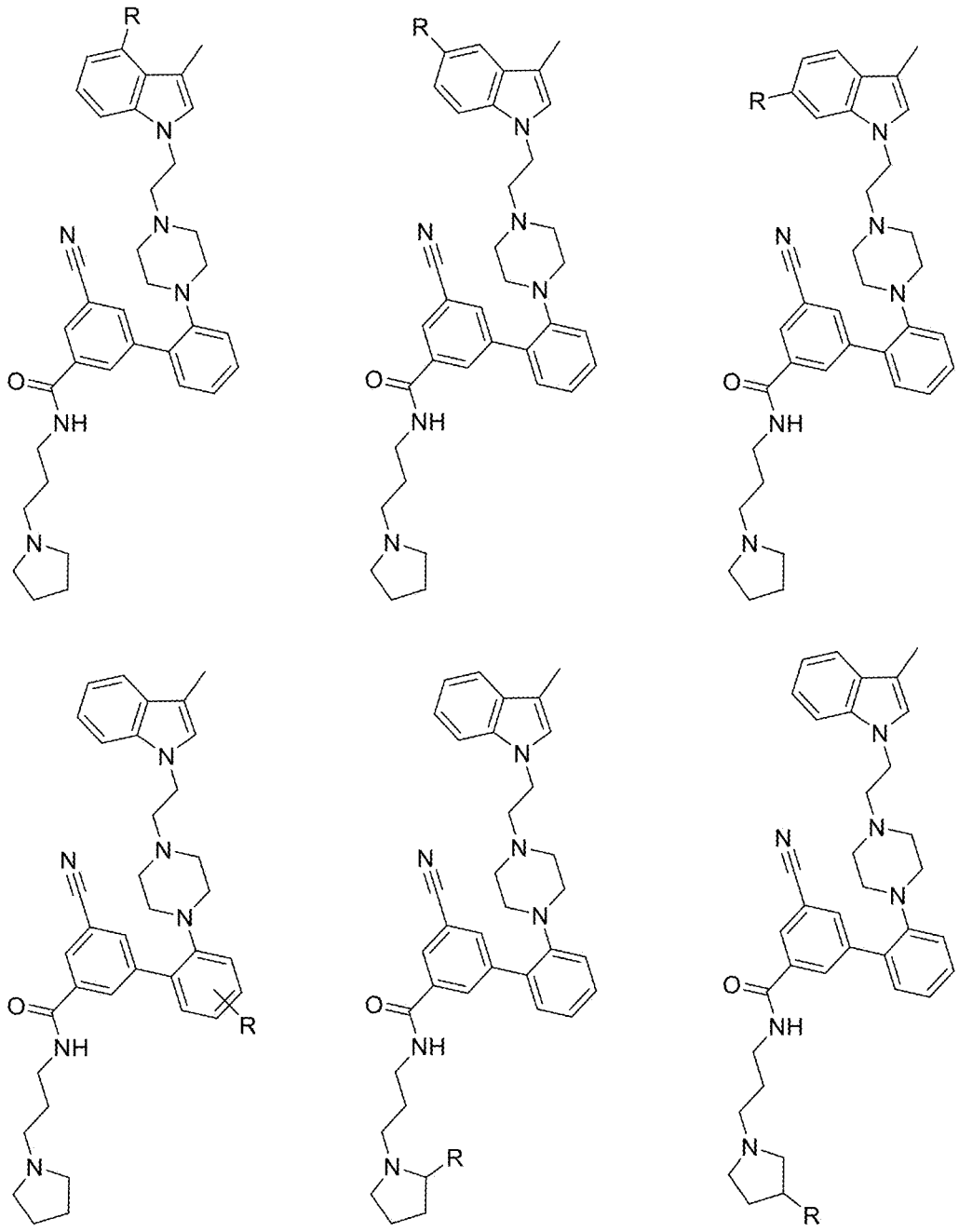


FIG. 4Q

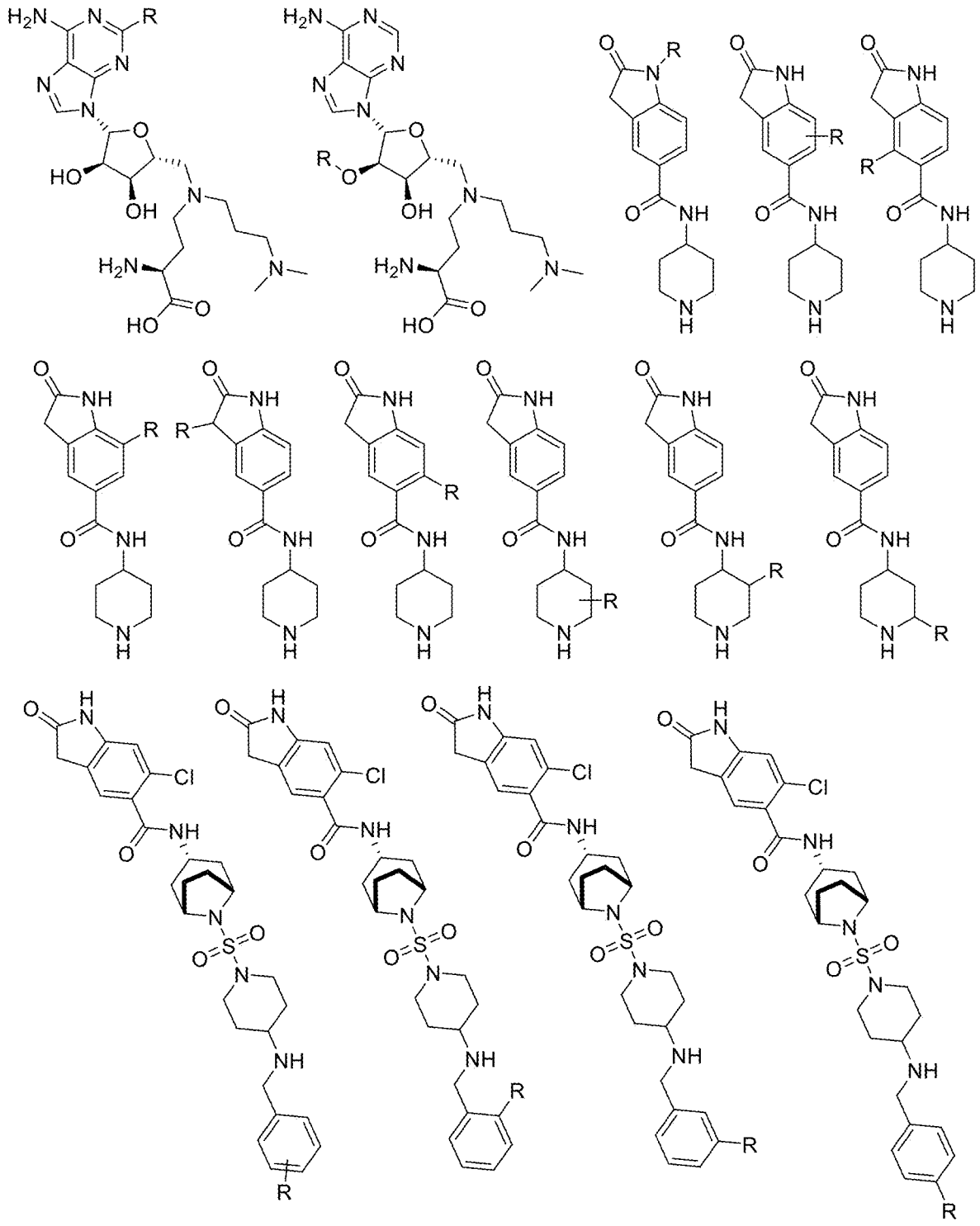


FIG. 4R

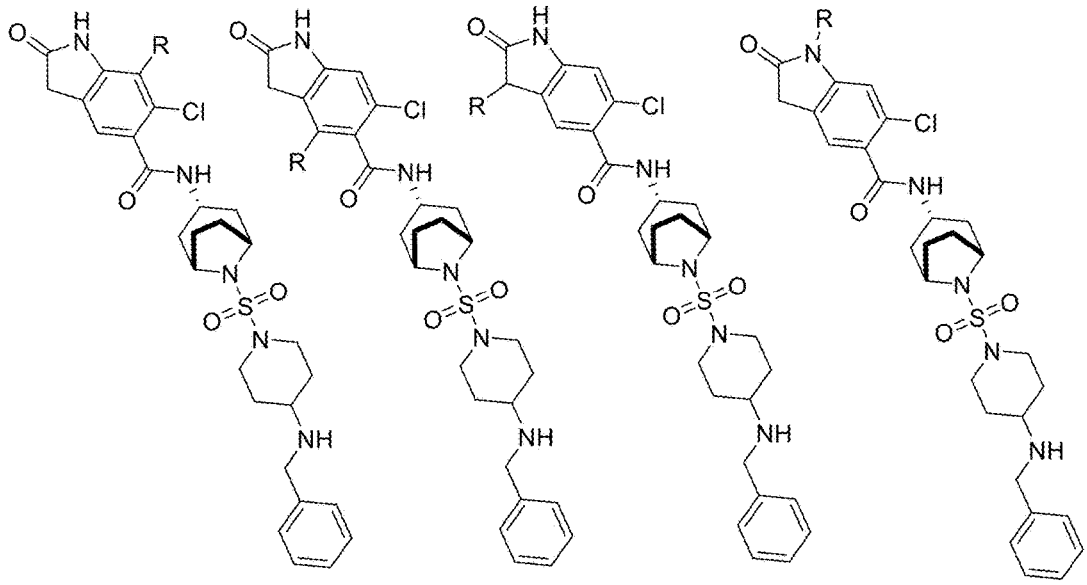


FIG. 4S

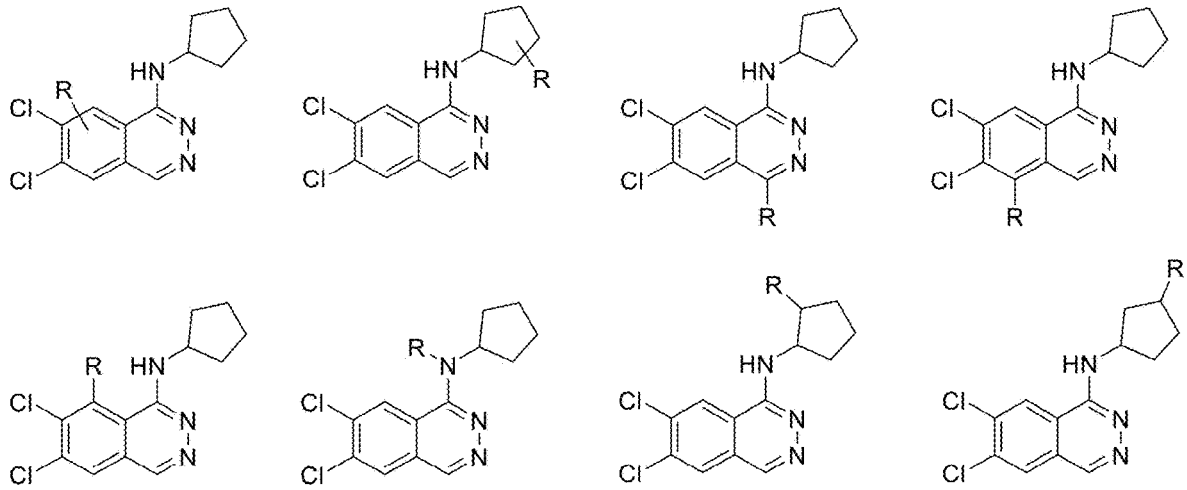


FIG. 4T

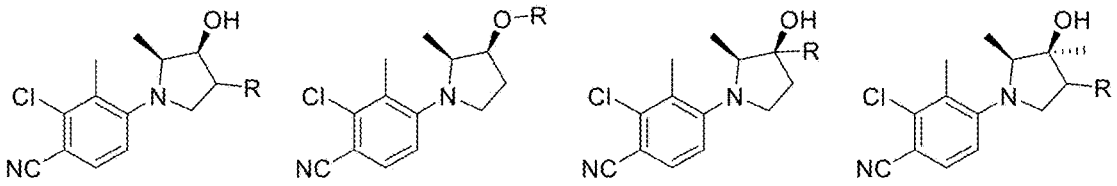


FIG. 4U

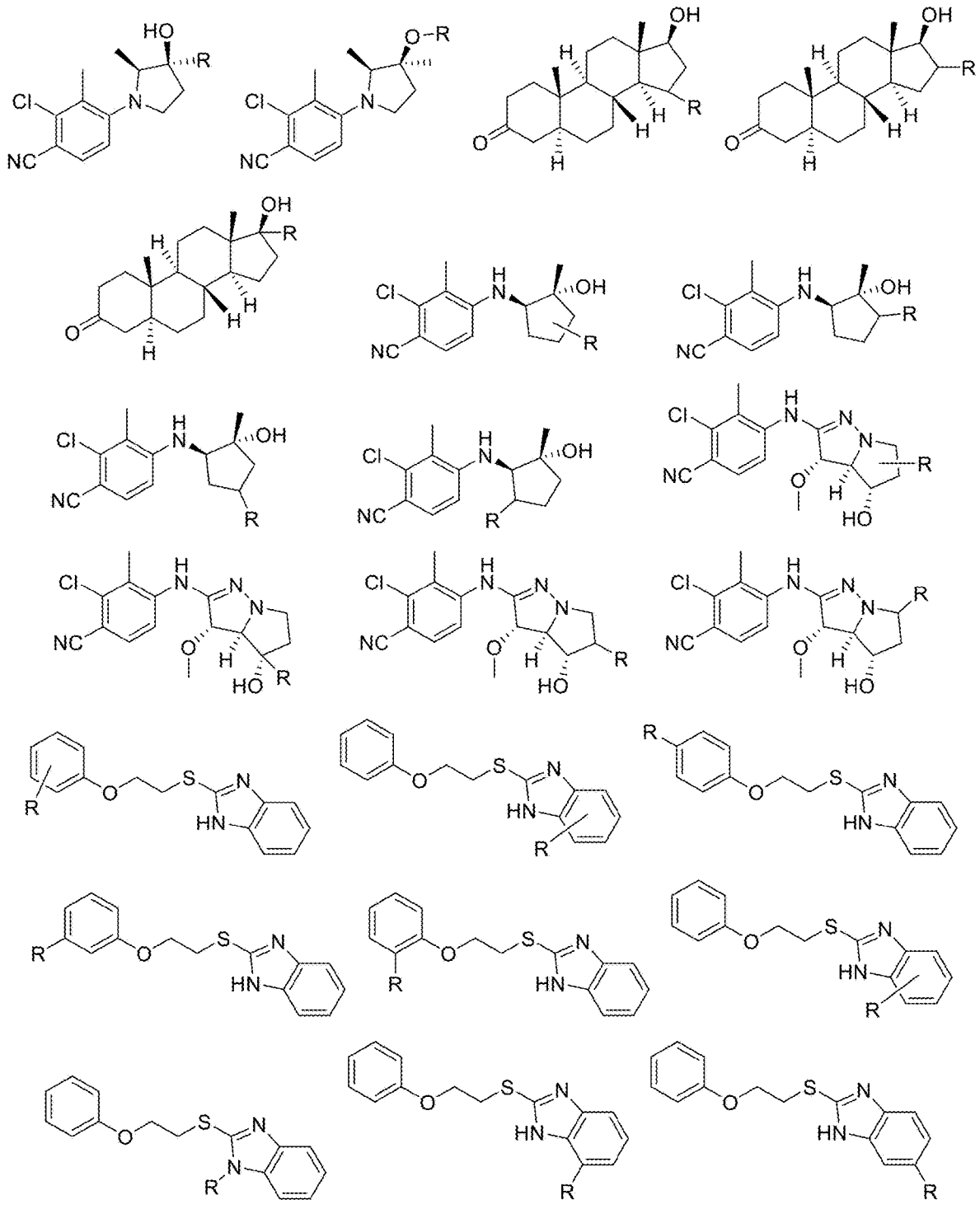


FIG. 4V

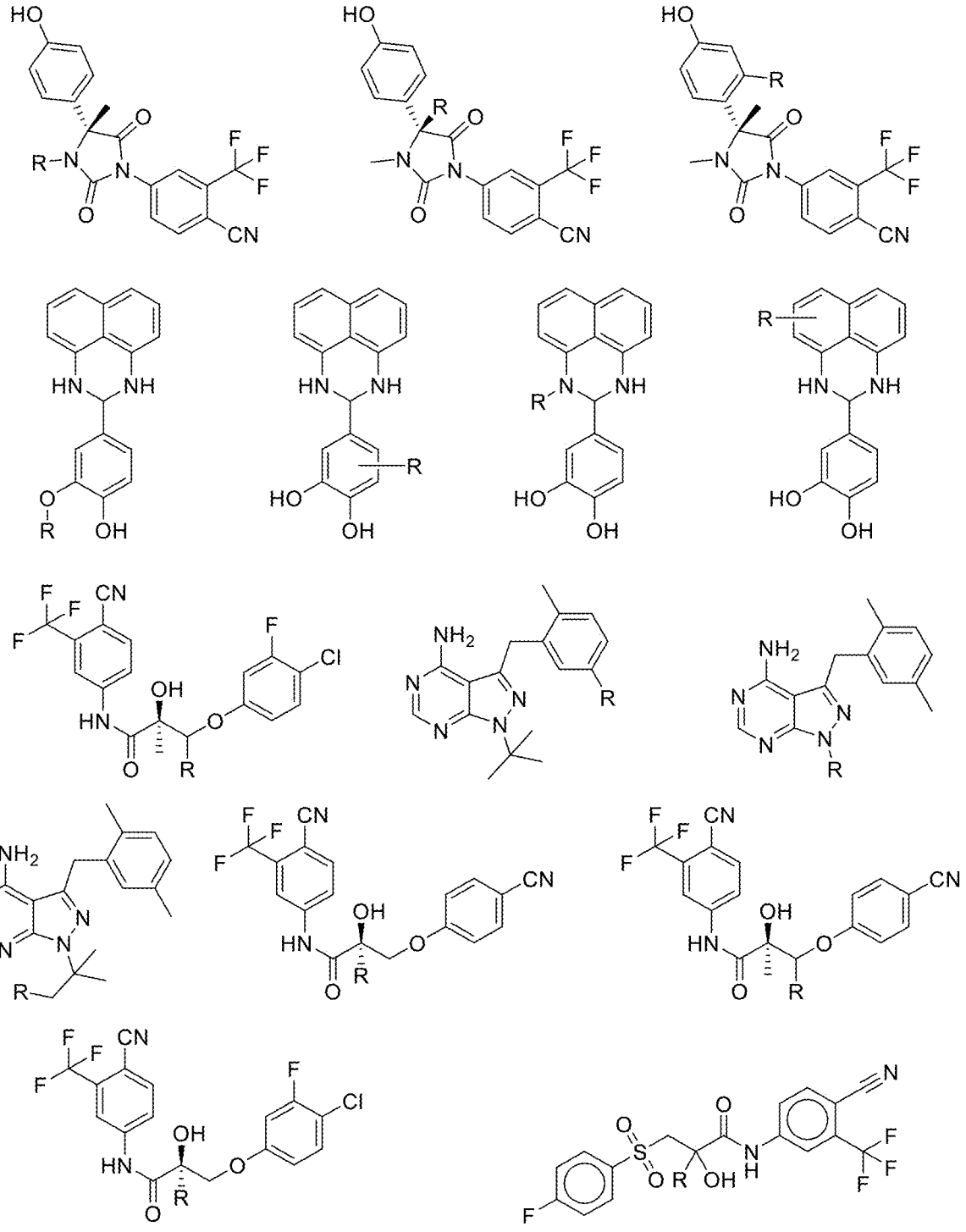


FIG. 4W

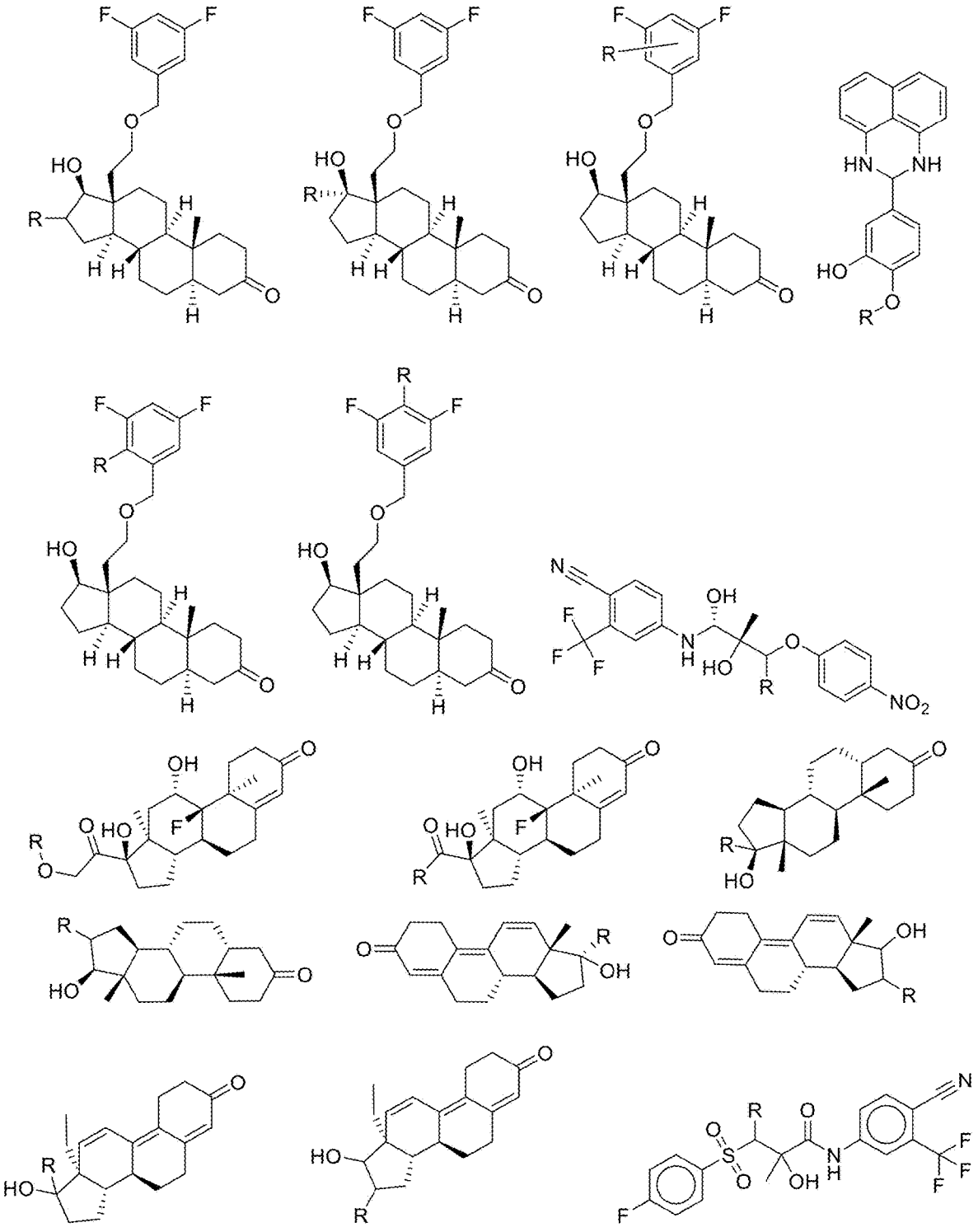


FIG. 4X

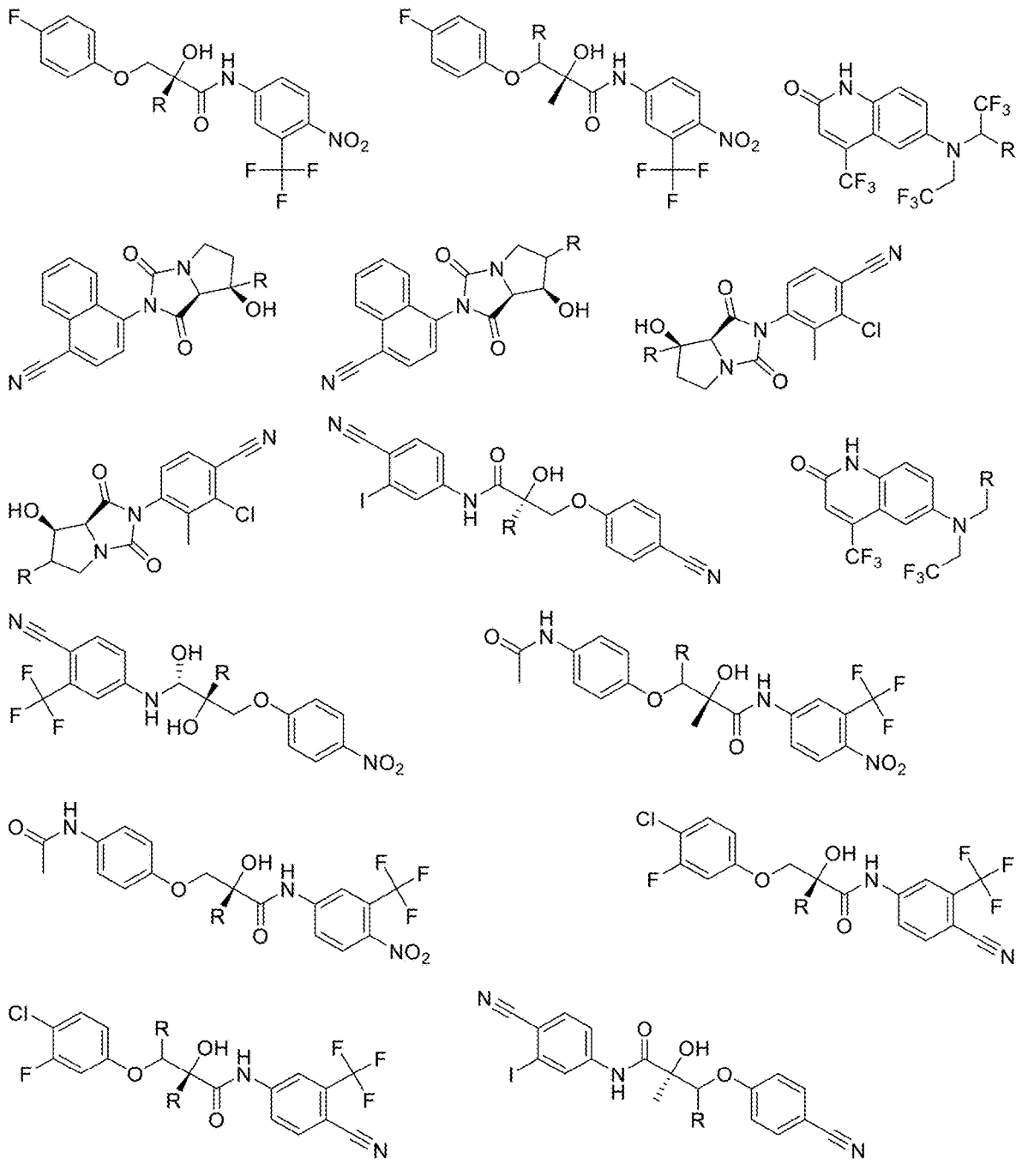


FIG. 4Y

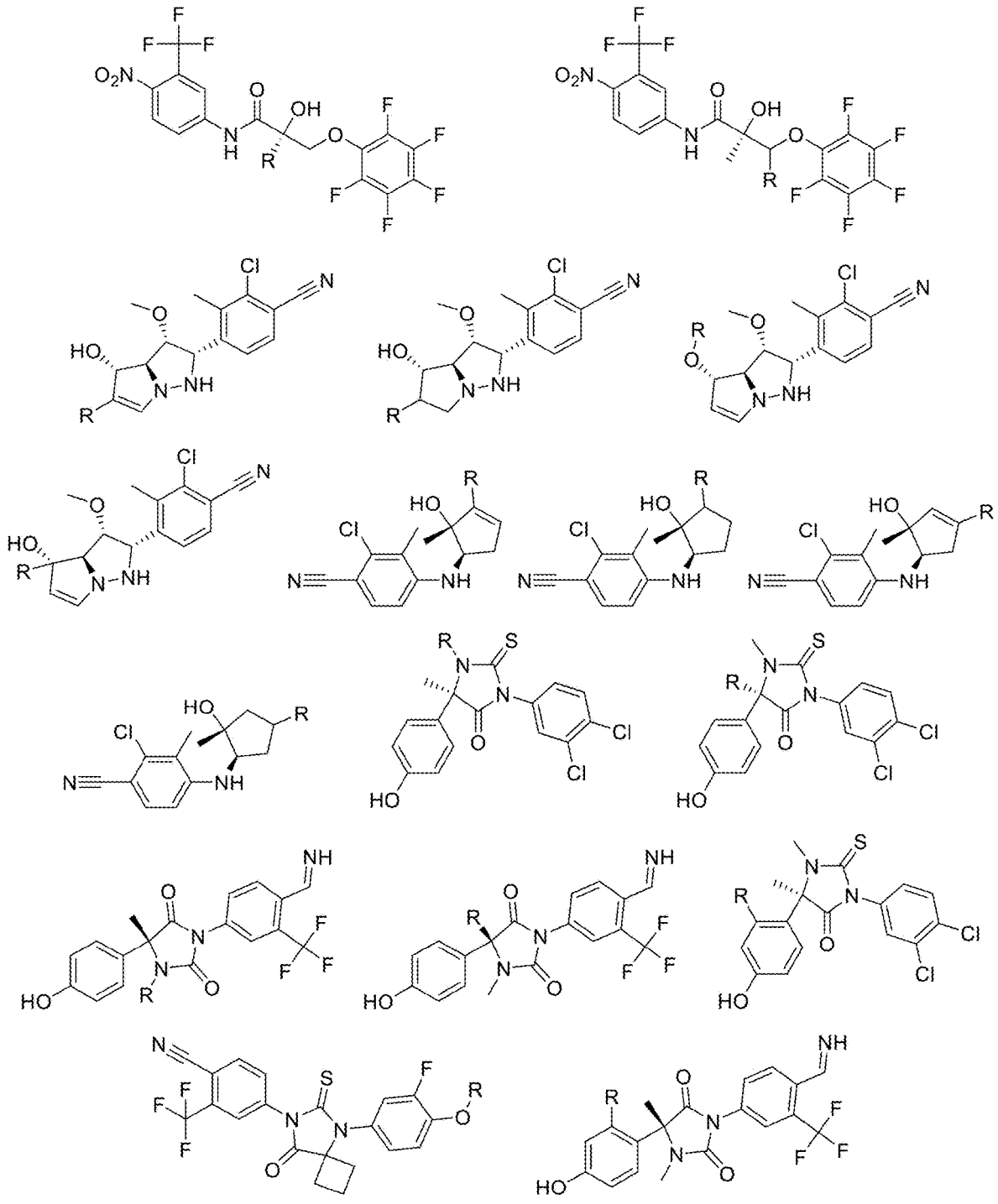


FIG. 4Z

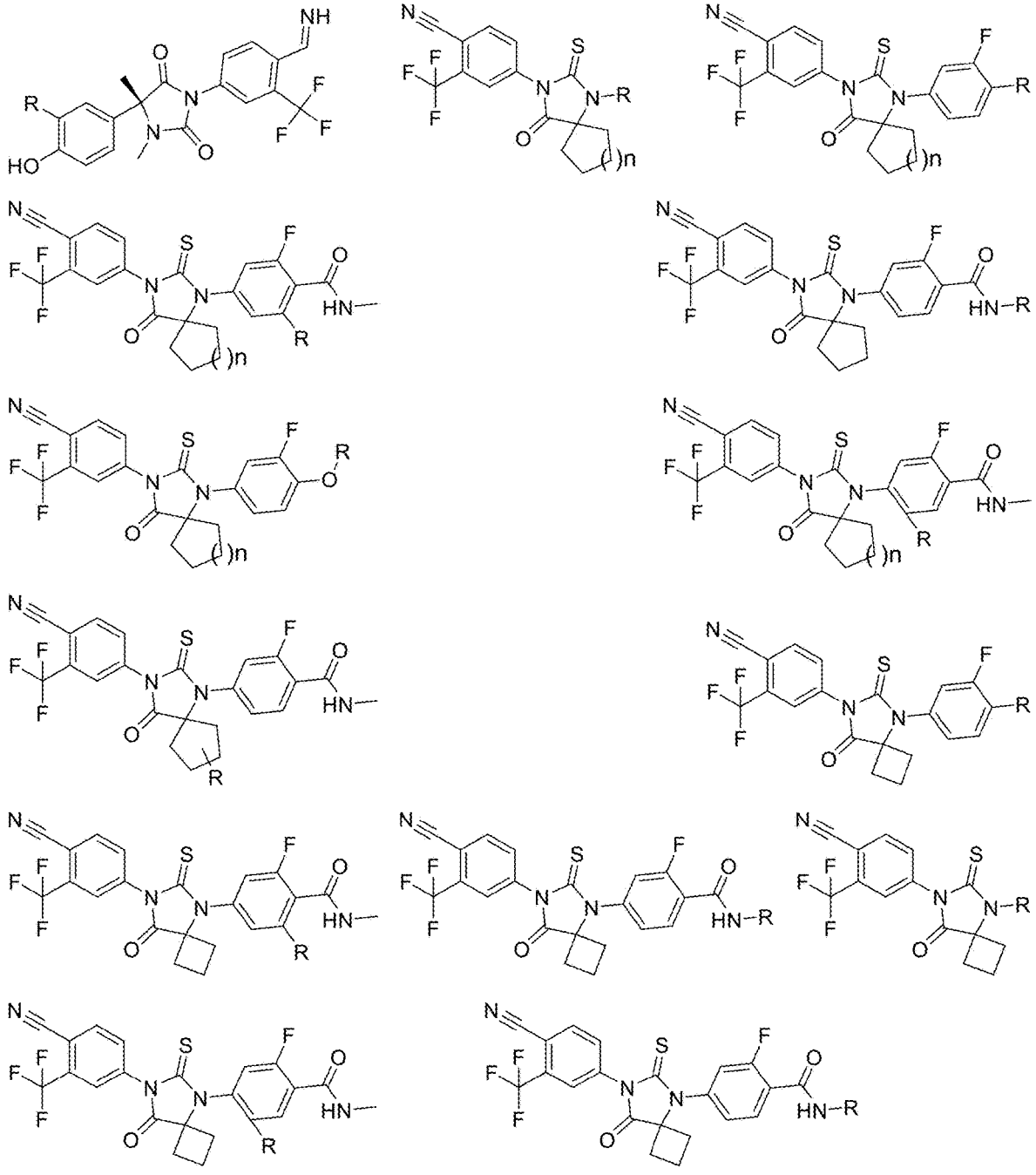


FIG. 4AA

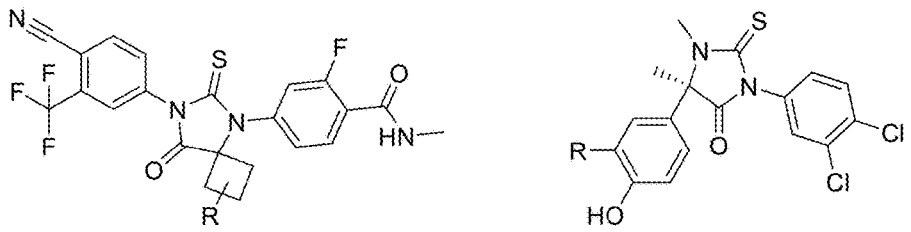


FIG. 4BB

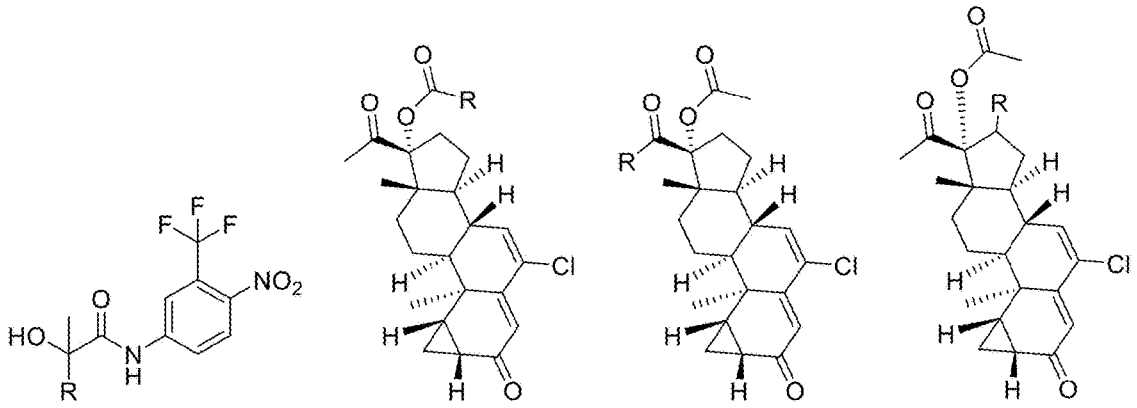


FIG. 4CC

FIG. 4DD

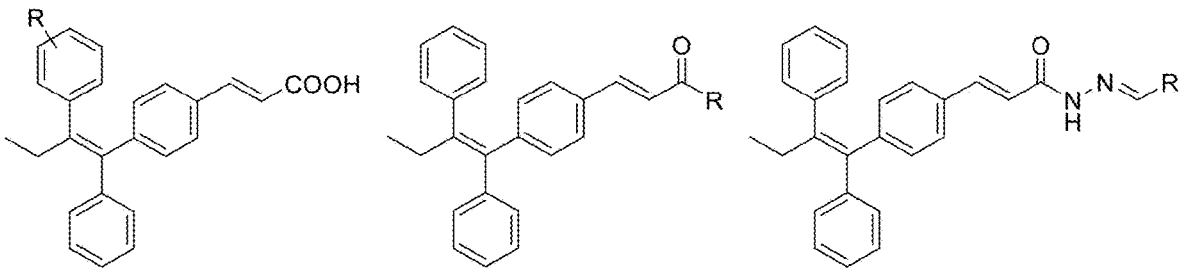


FIG. 4EE

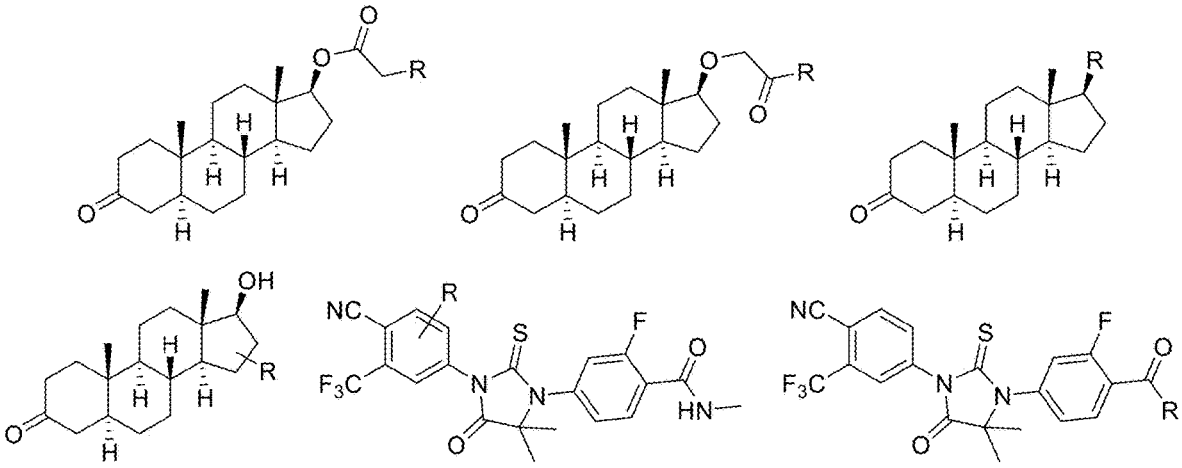


FIG. 5A

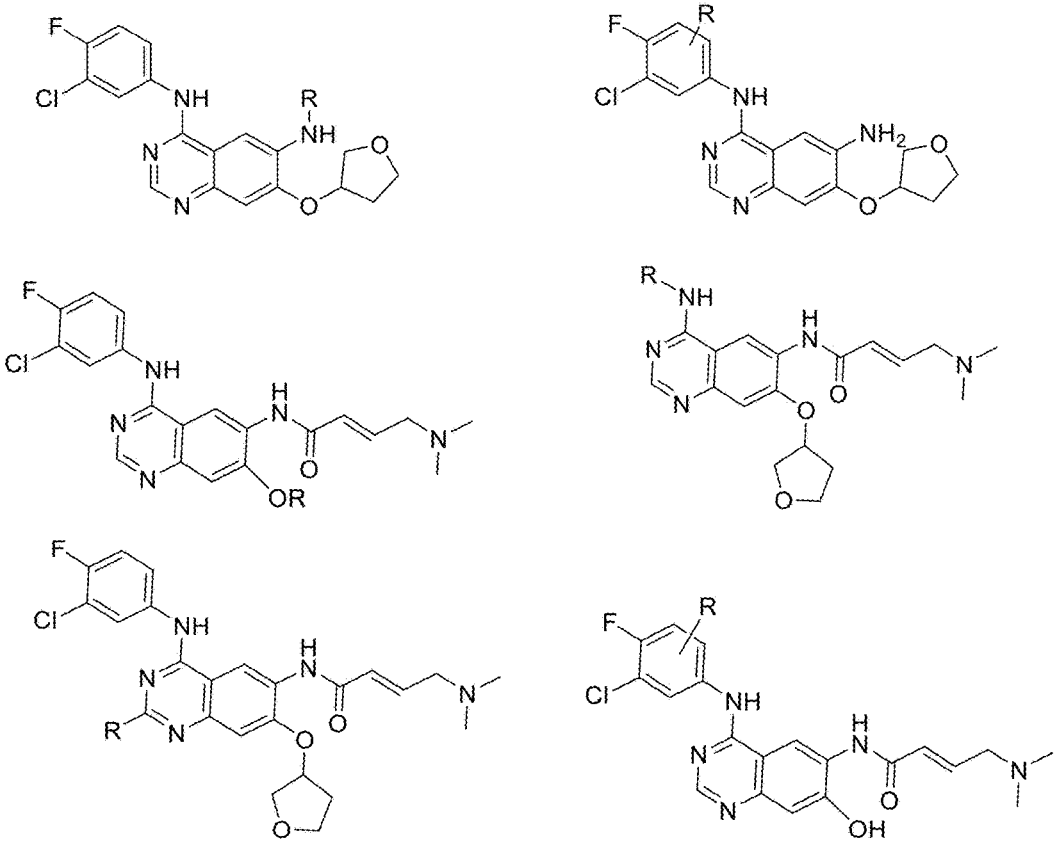


FIG. 5B

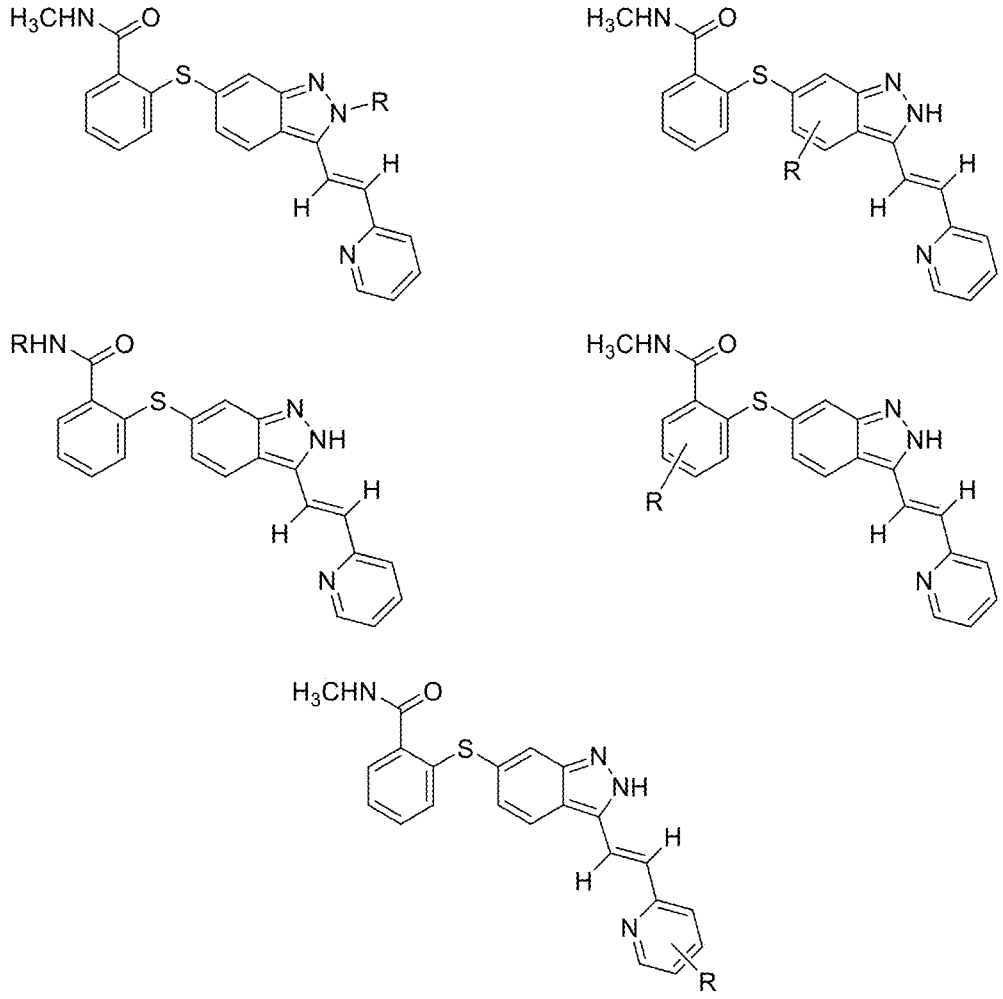


FIG. 5C

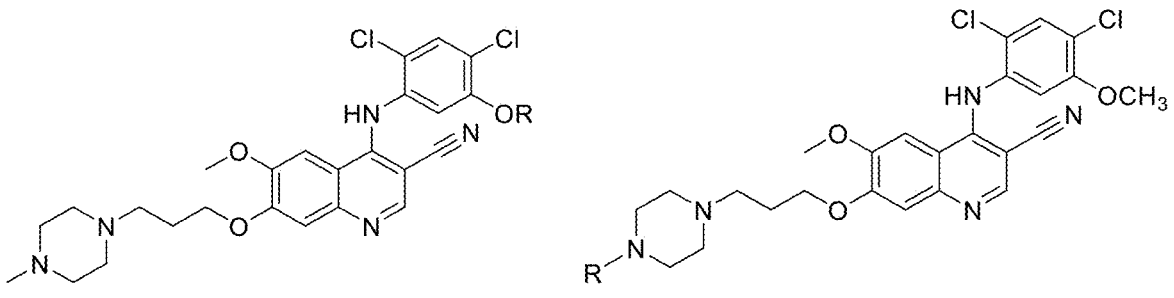


FIG. 5D

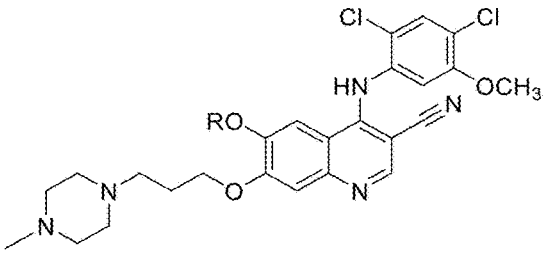
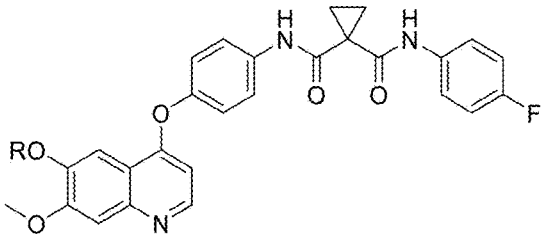
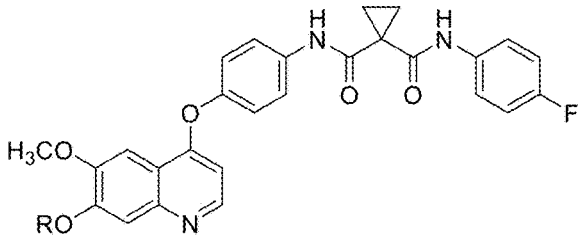
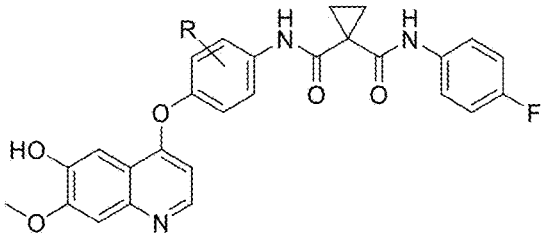
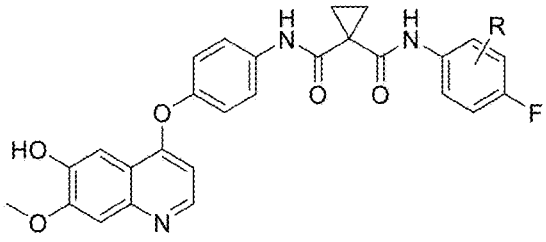


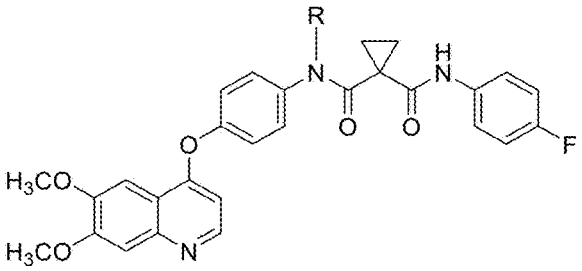
FIG. 5E











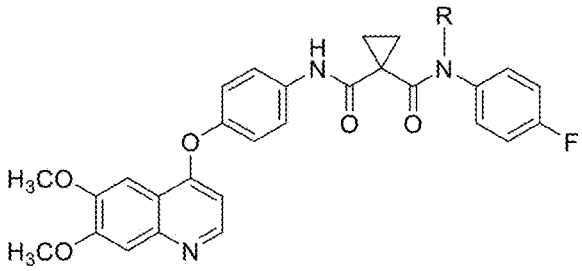


FIG. 5F

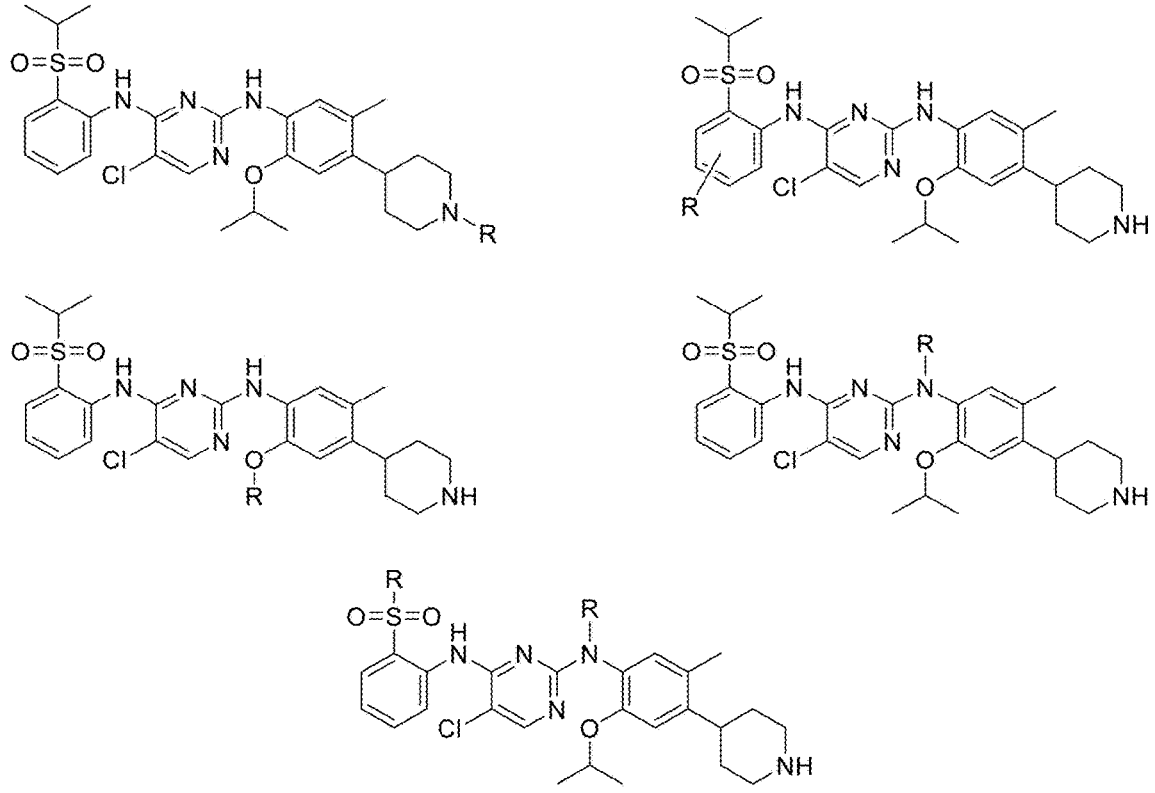


FIG. 5G

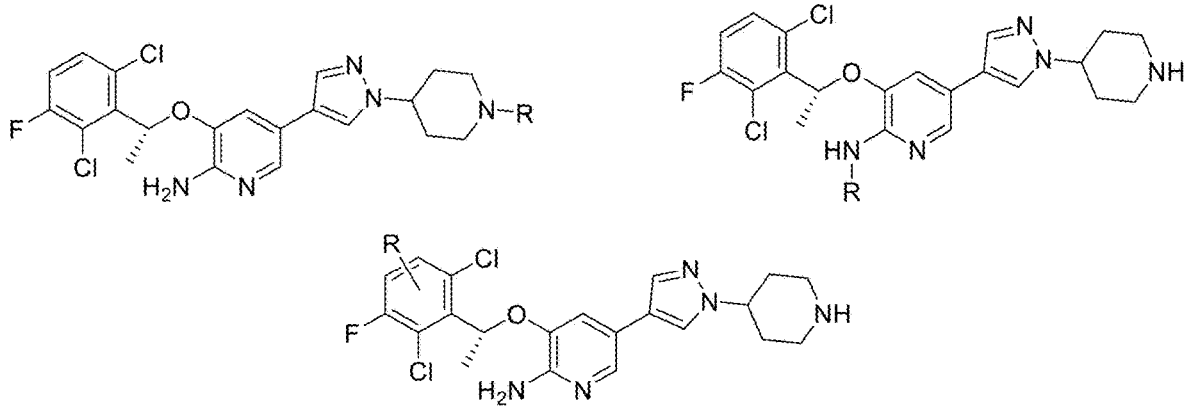


FIG. 5H

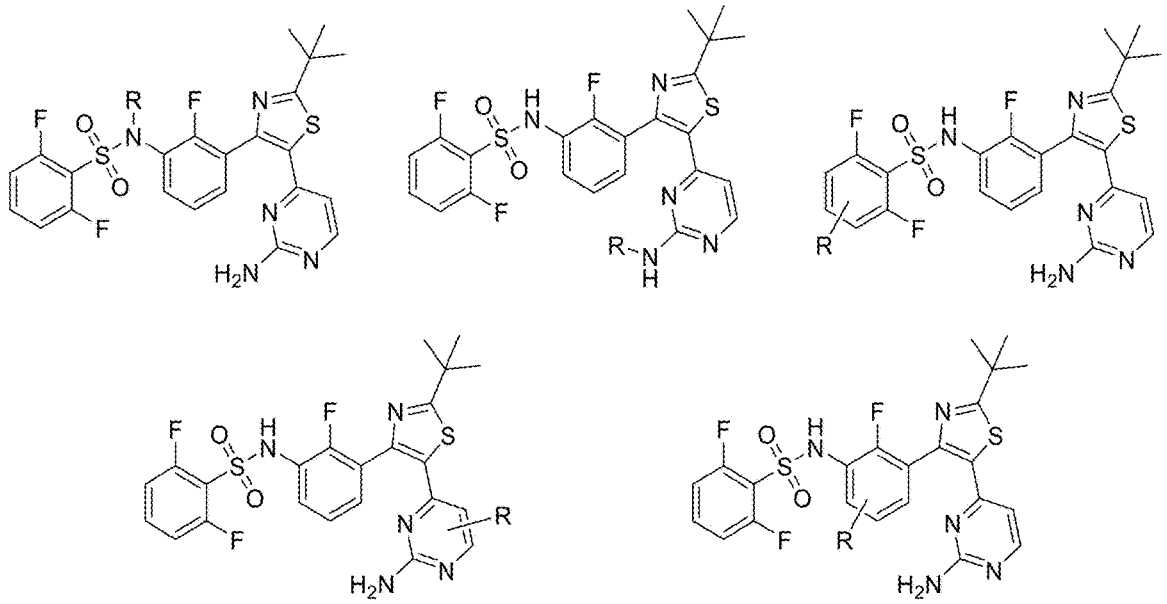


FIG. 5I

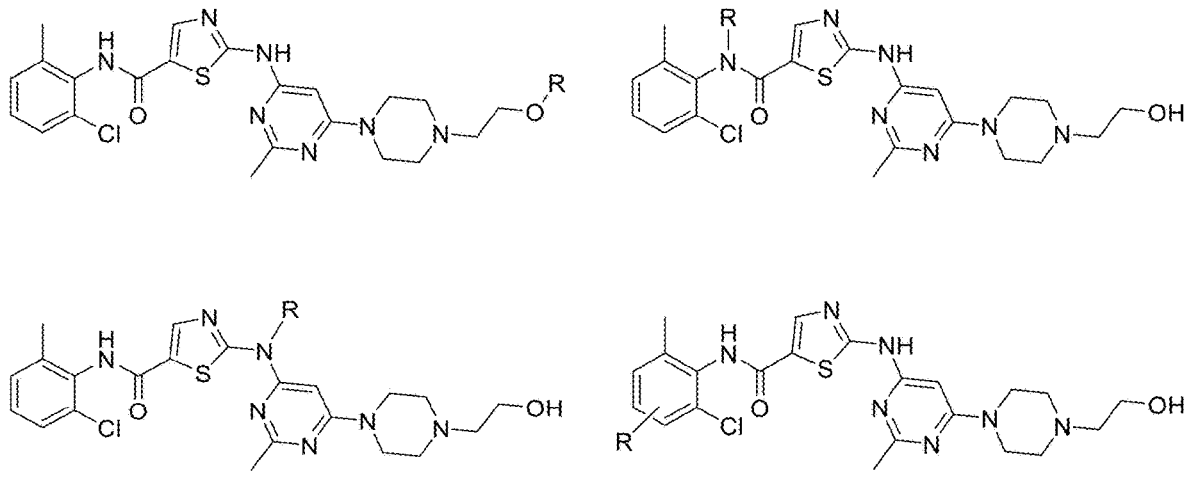


FIG. 5J

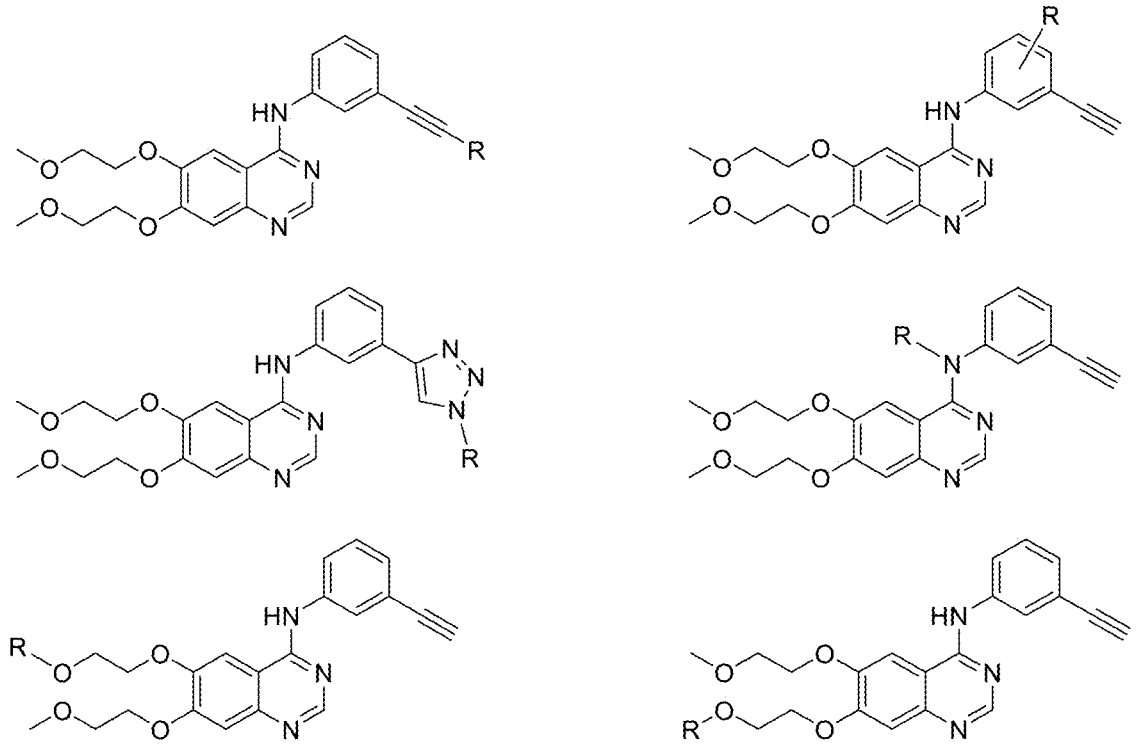


FIG. 5K

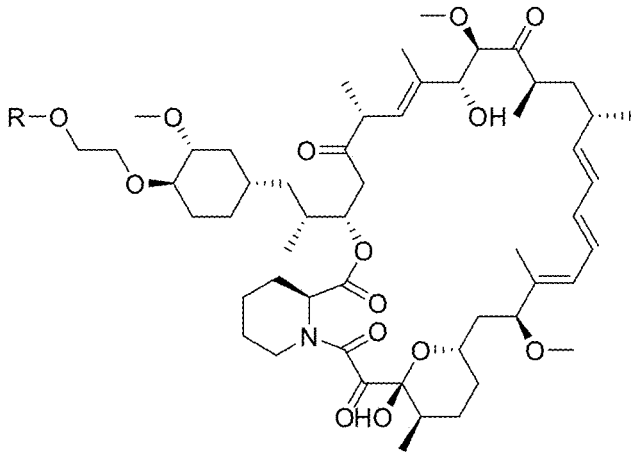


FIG. 5L

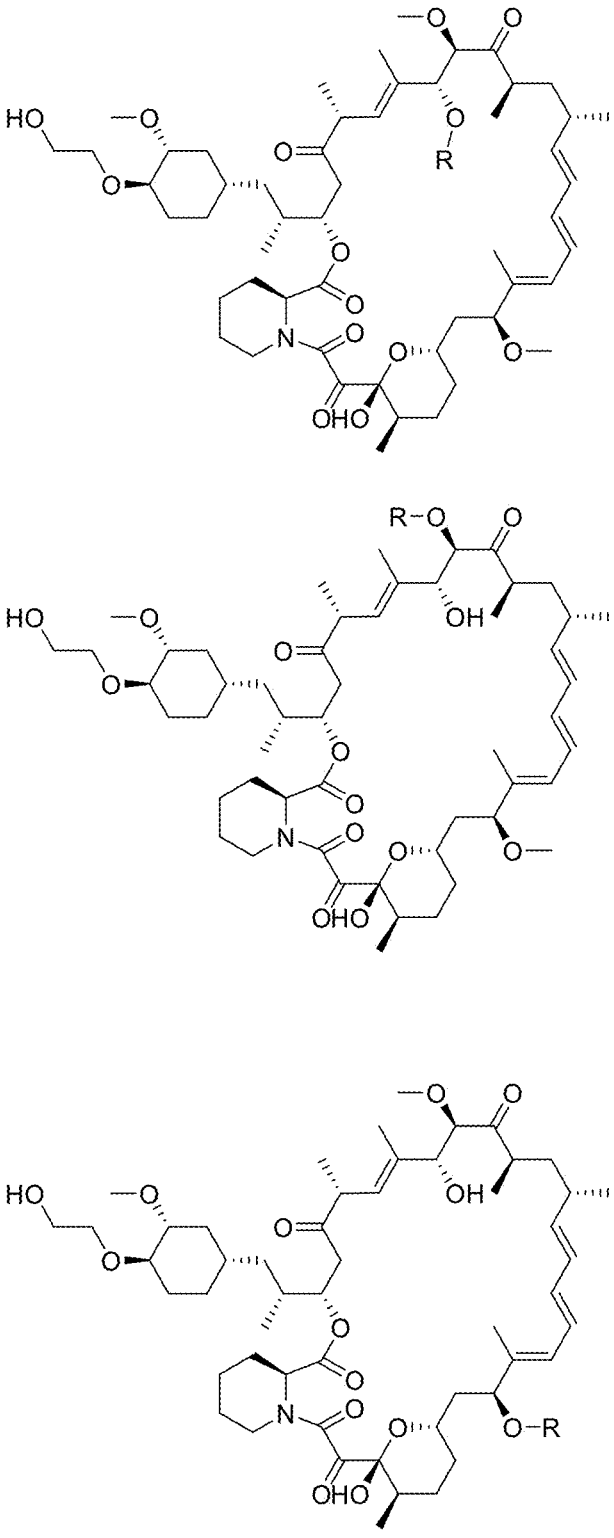


FIG. 5M

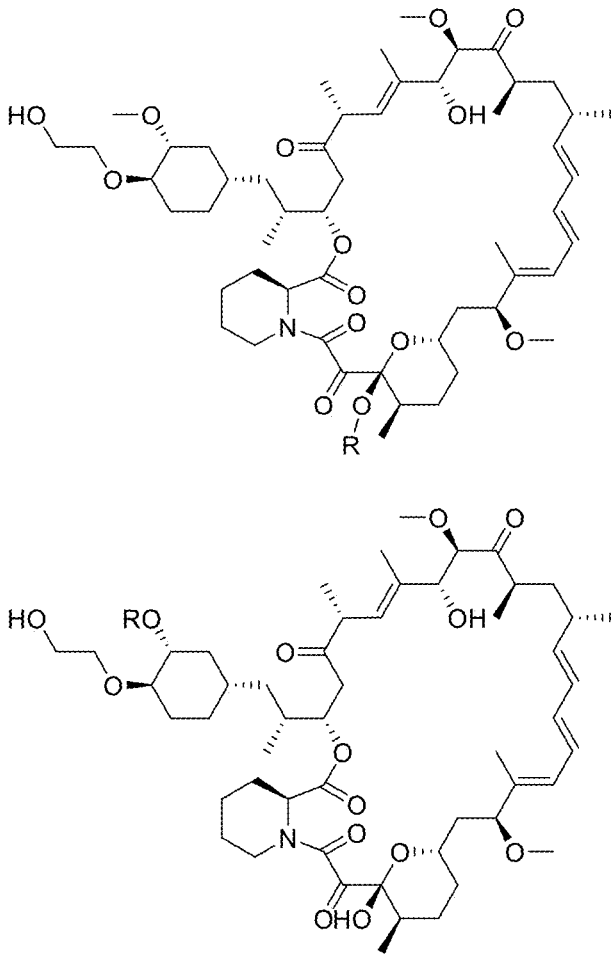


FIG. 5N

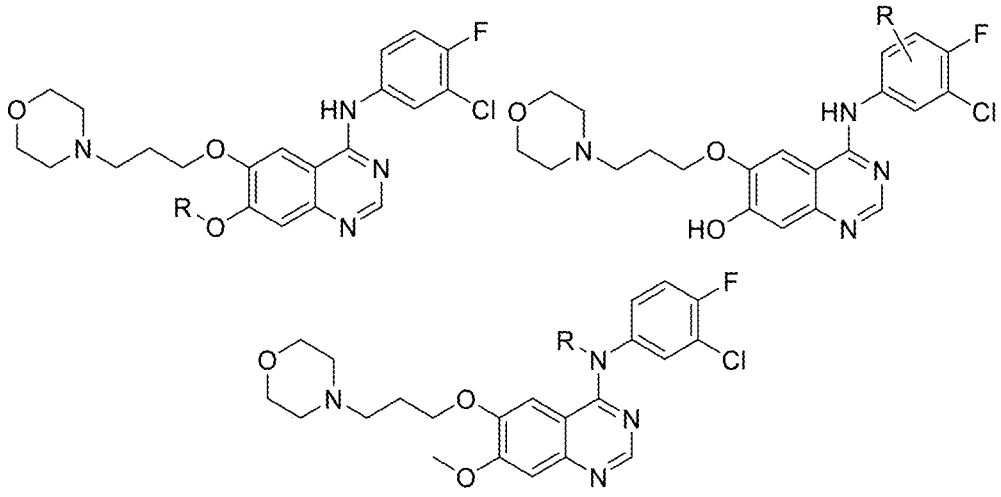


FIG. 5O

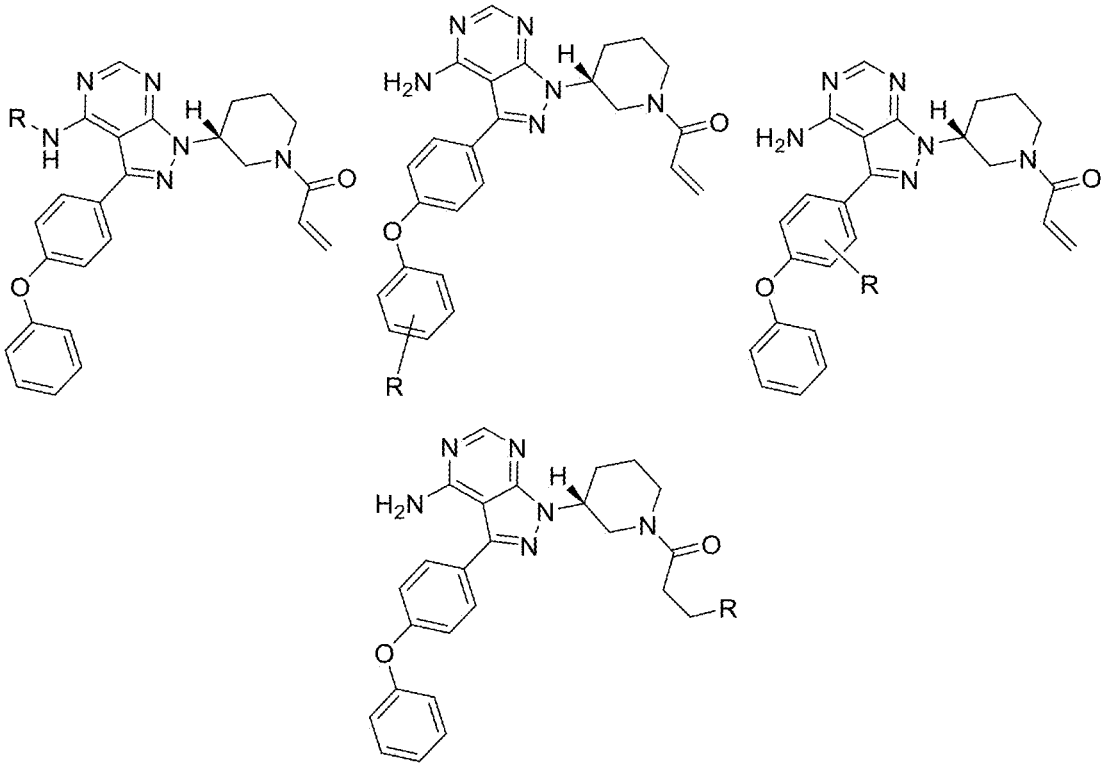


FIG. 5P

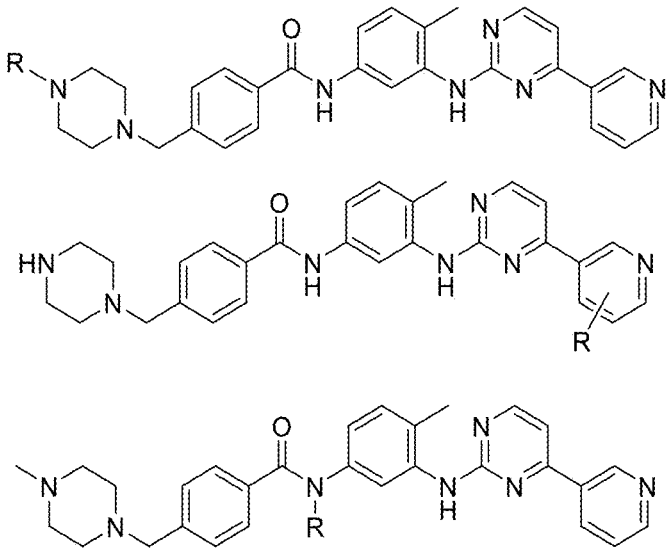


FIG. 5Q

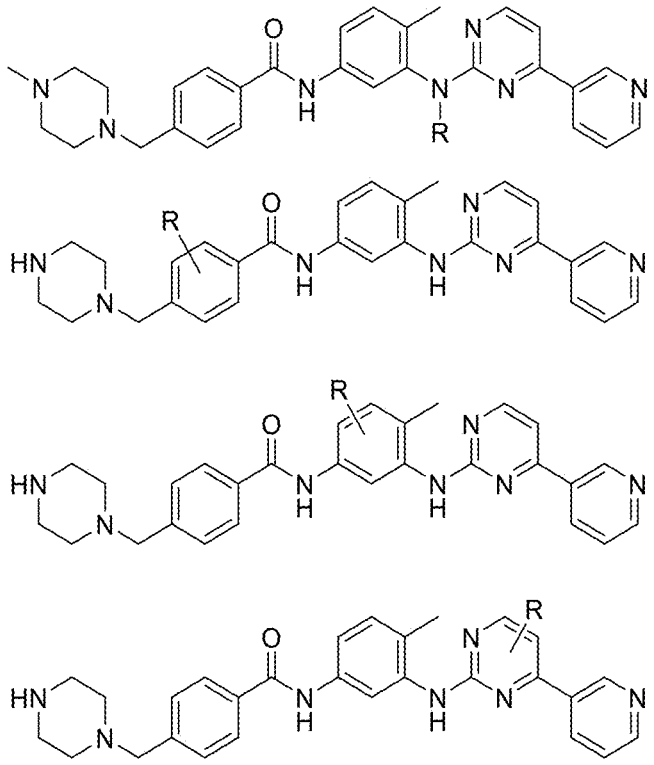


FIG. 5R

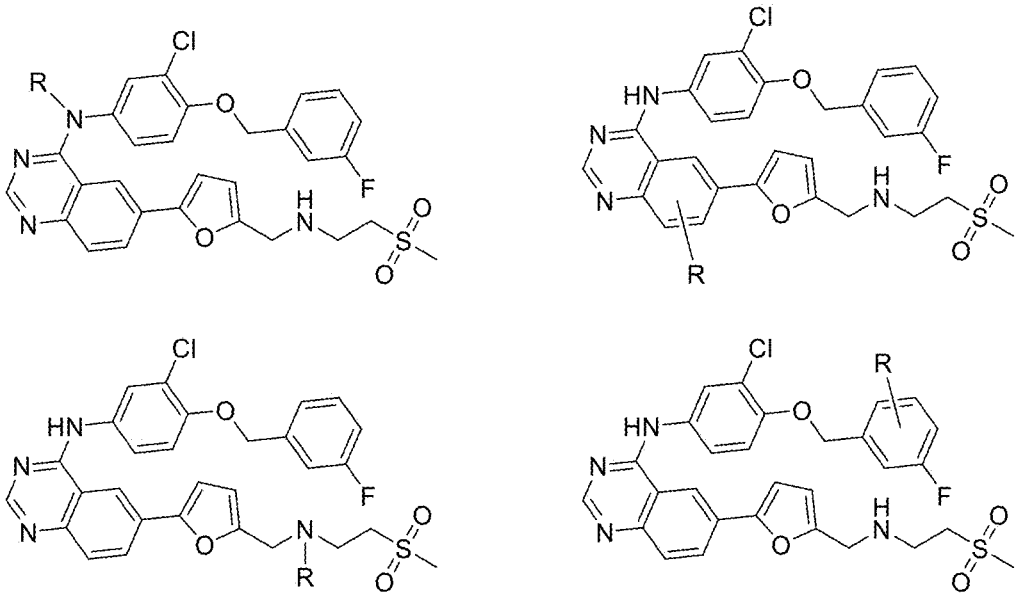


FIG. 5S

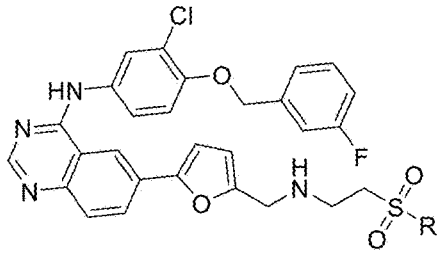
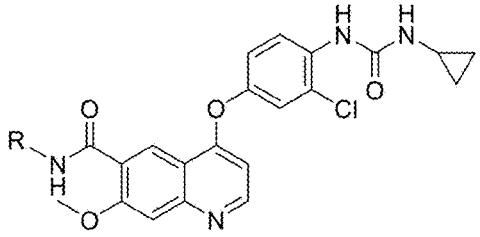
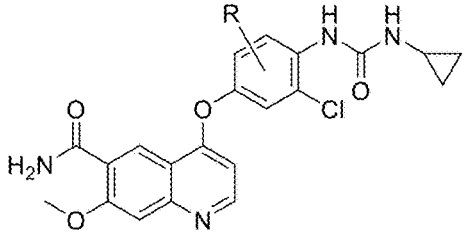
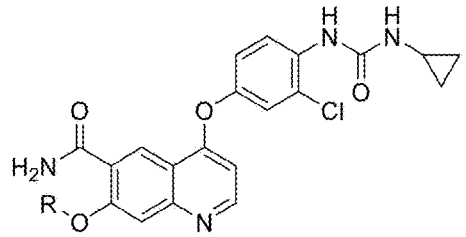
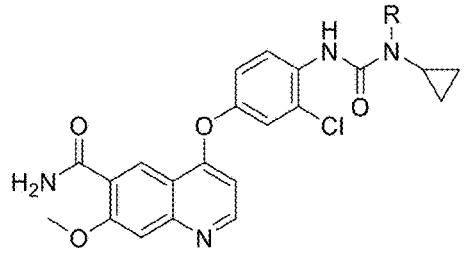


FIG. 5T









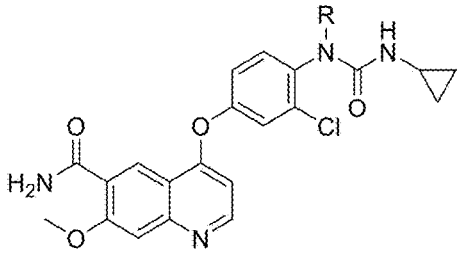
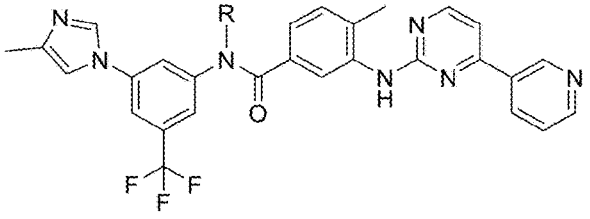


FIG. 5U



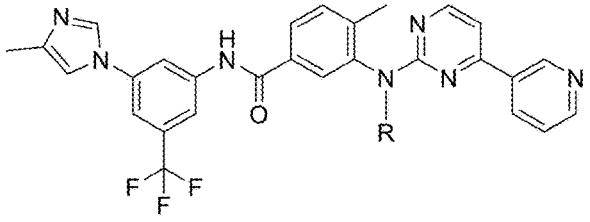


FIG. 5V

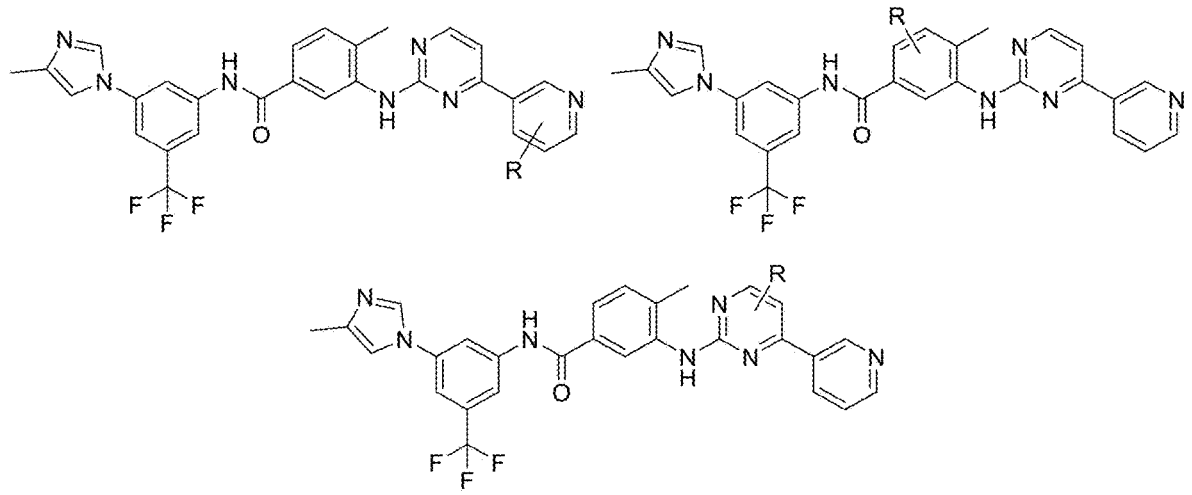


FIG. 5W

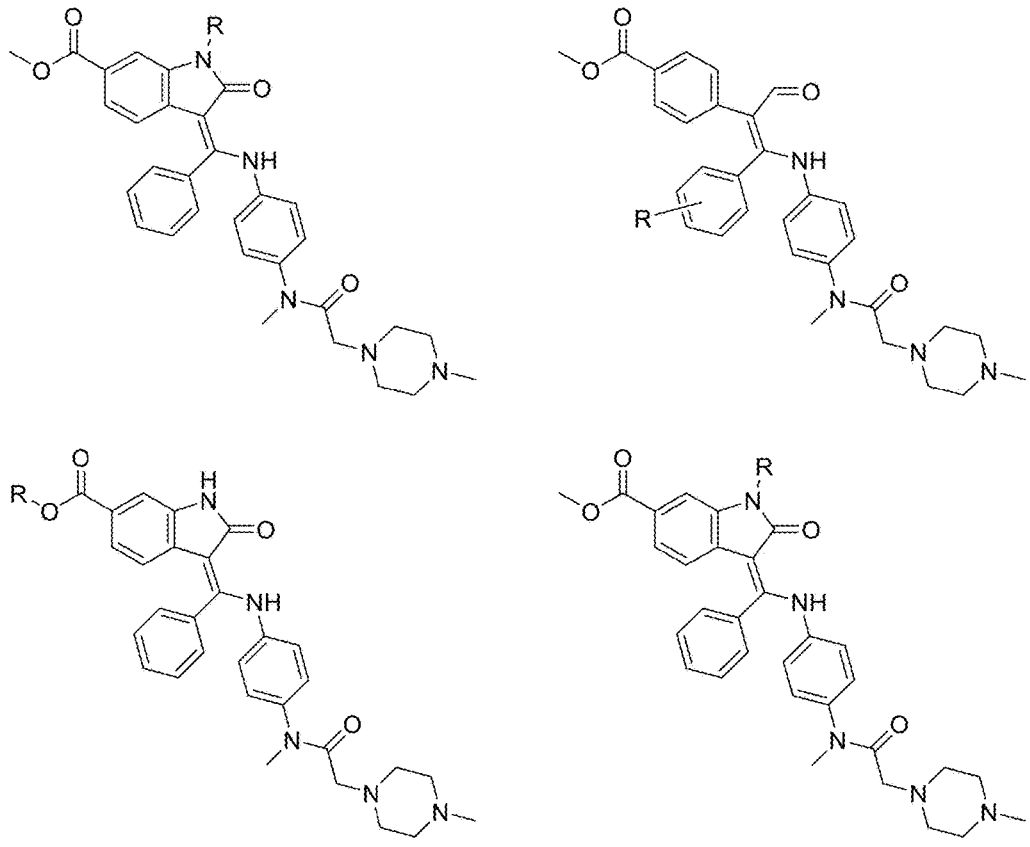


FIG. 5X

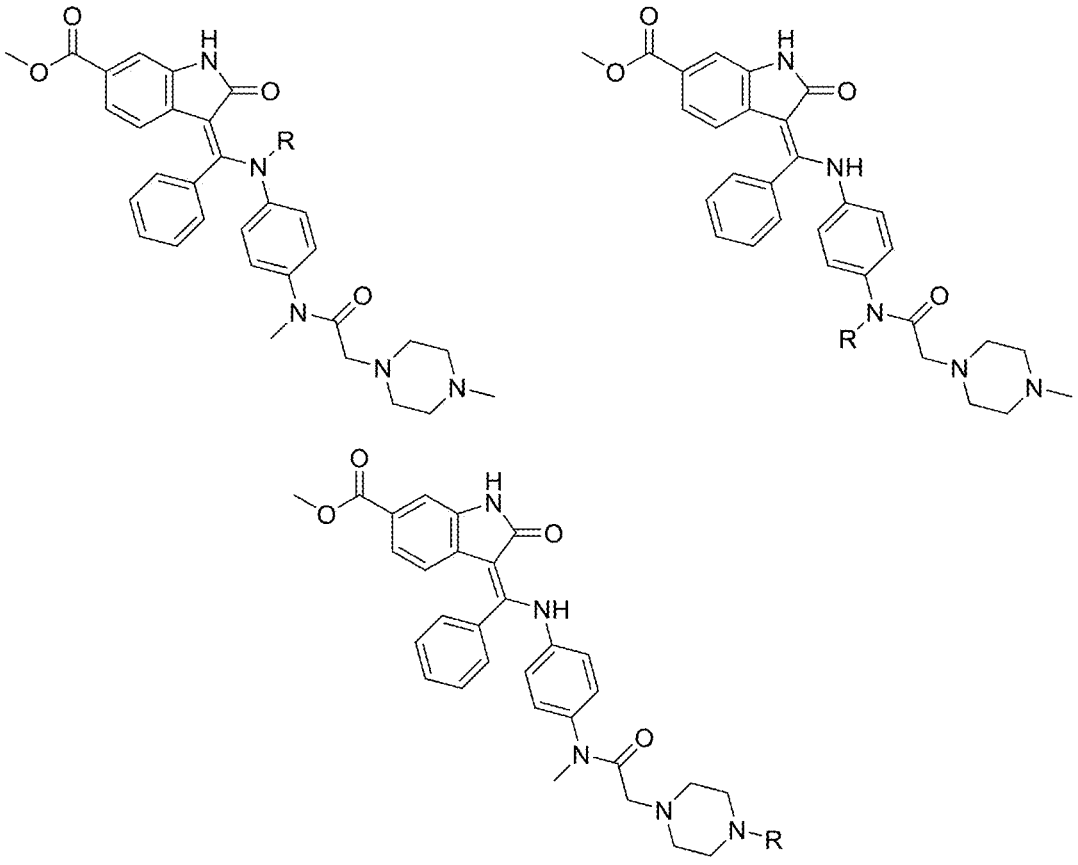


FIG. 5Y

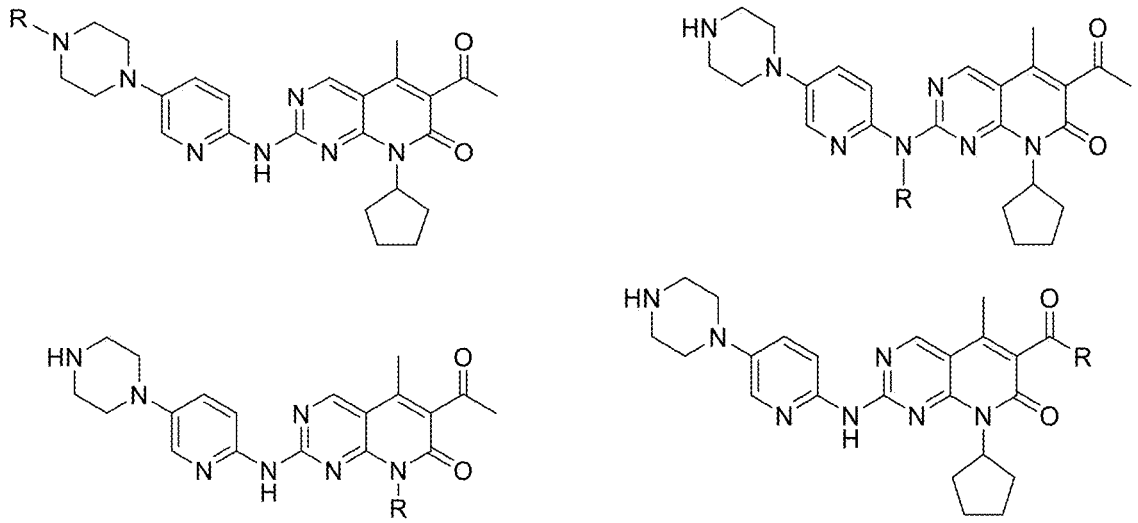


FIG. 5Z

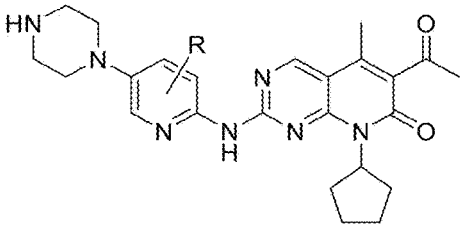


FIG. 5AA

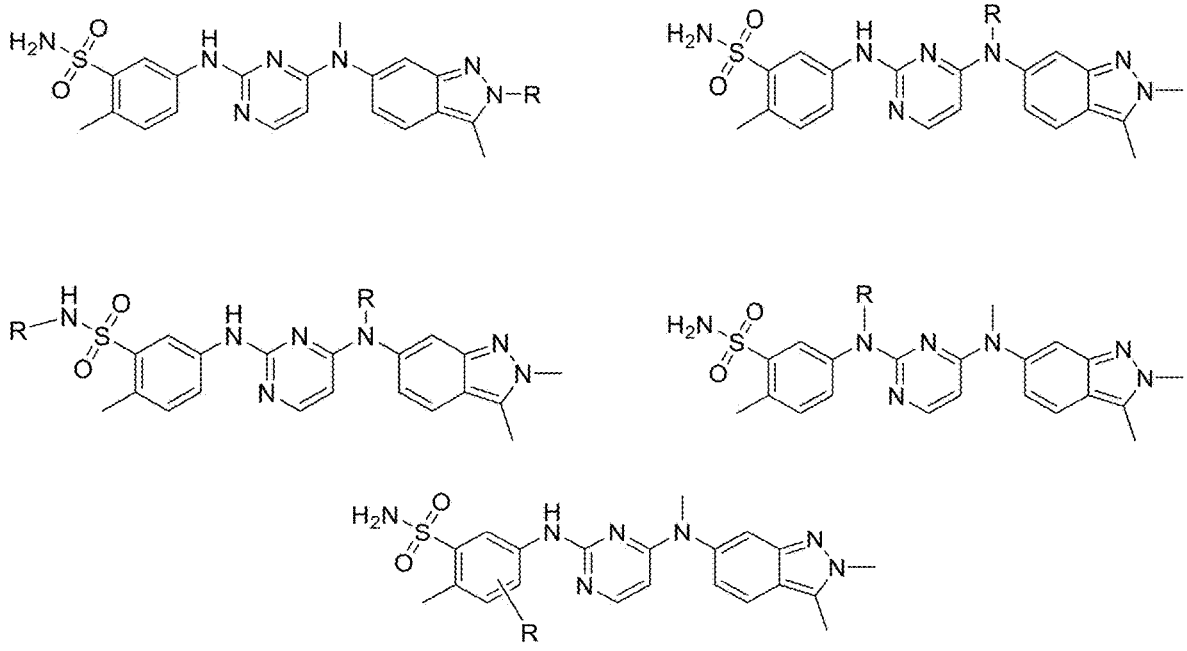


FIG. 5BB

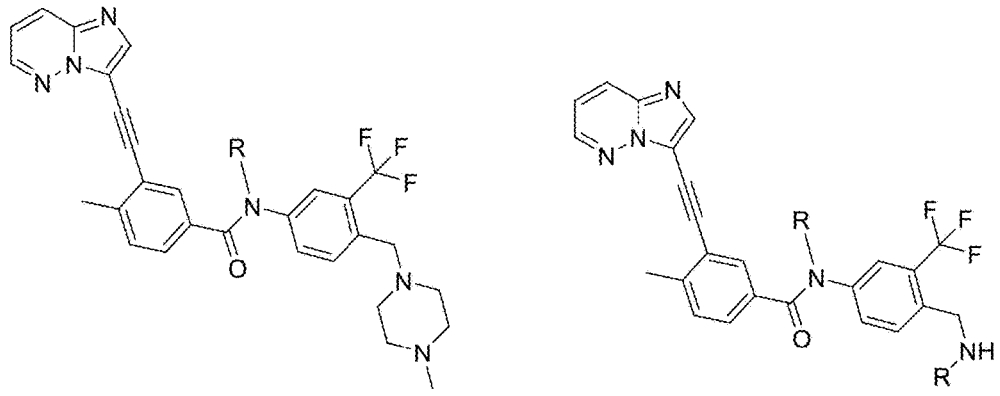


FIG. 5CC

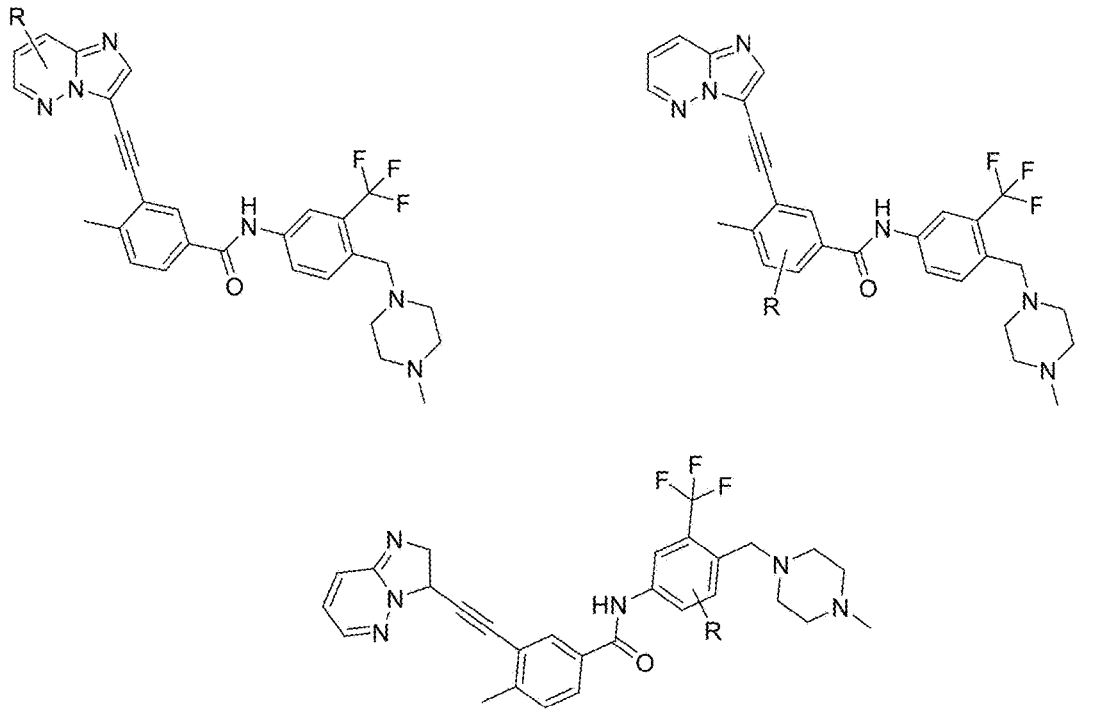


FIG. 5DD

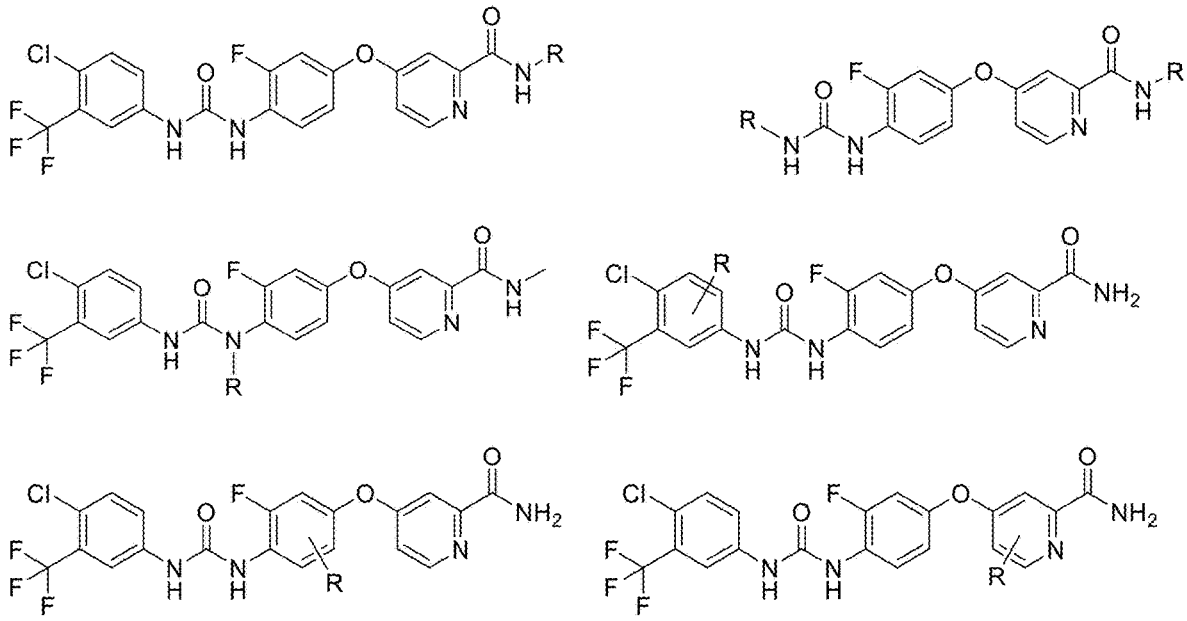


FIG. 5EE

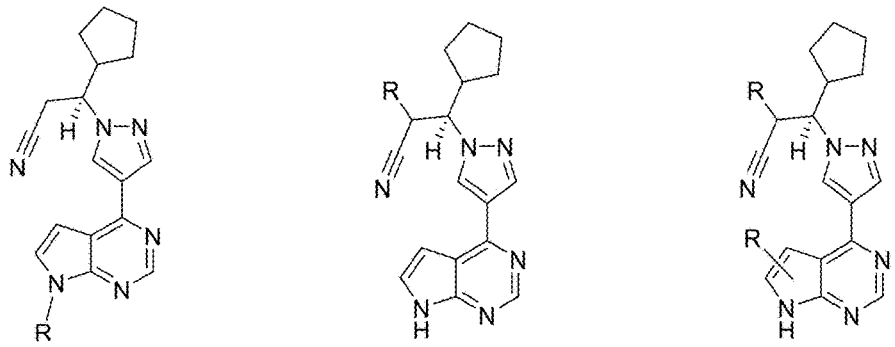


FIG. 5FF

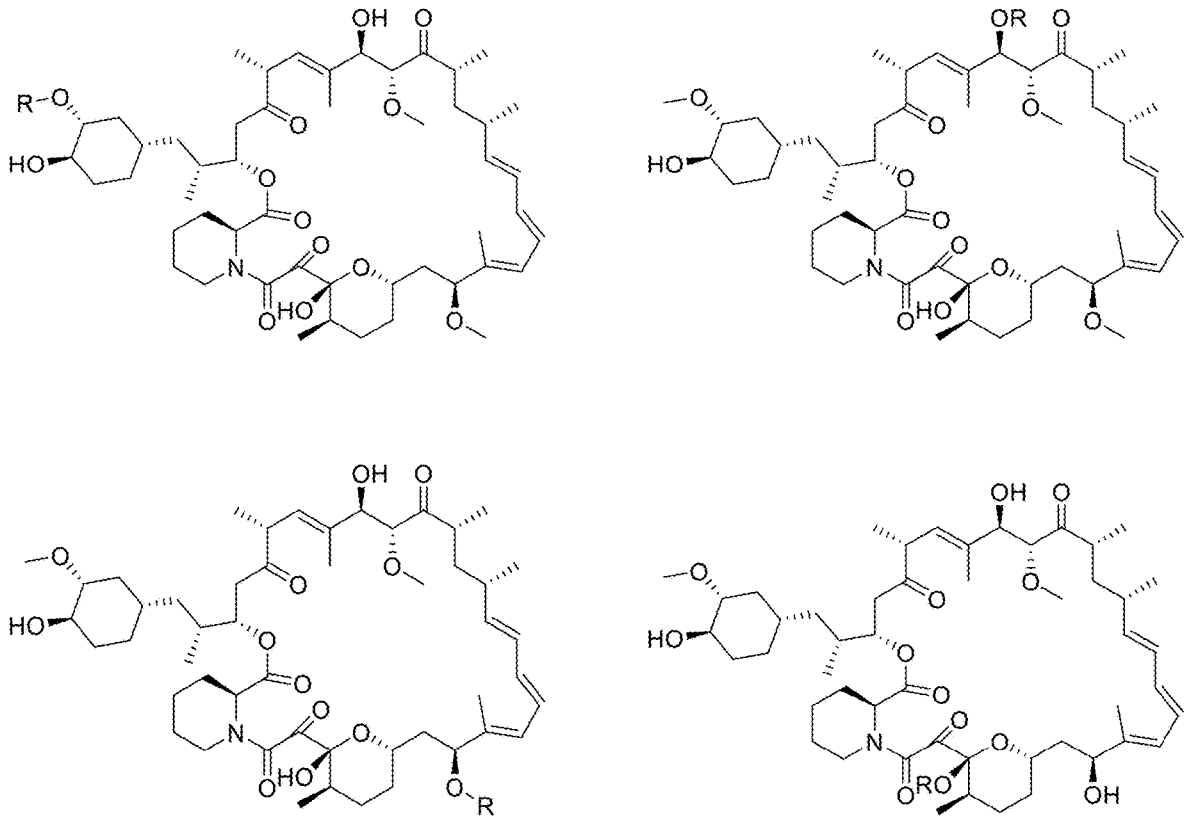


FIG. 5GG

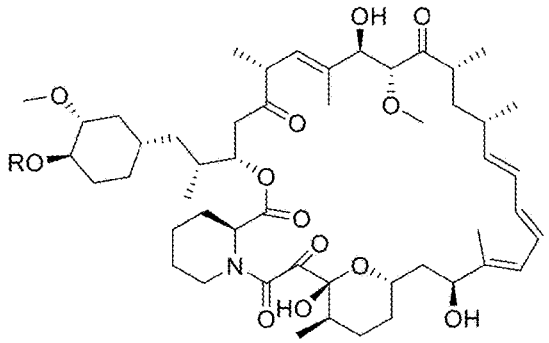


FIG. 5HH

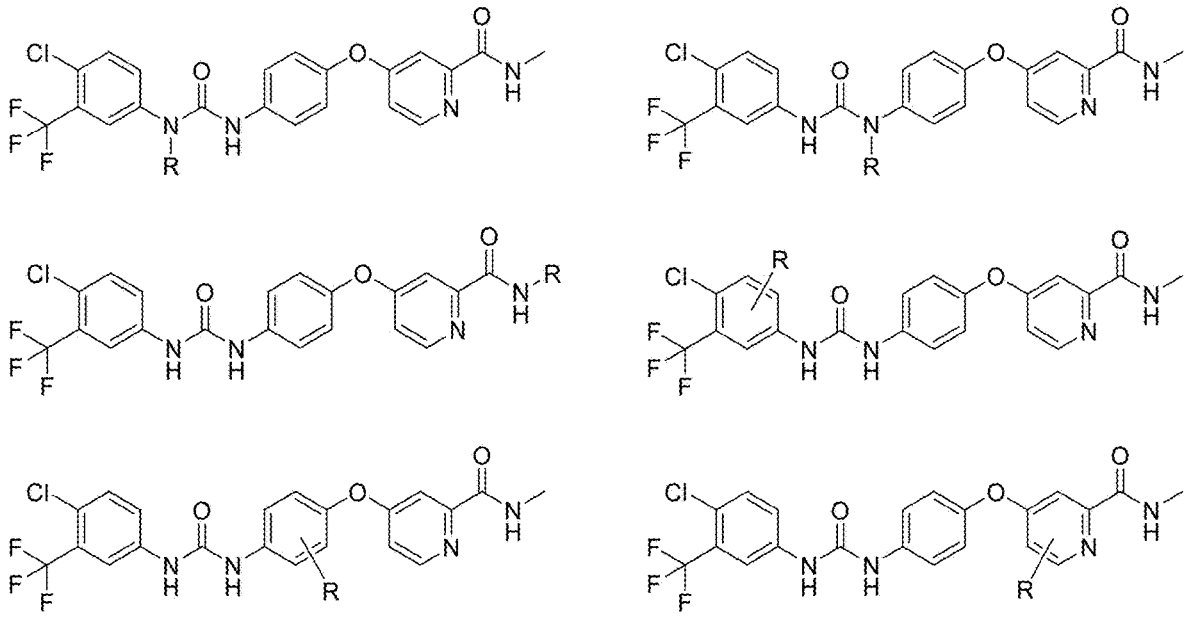


FIG. 5II

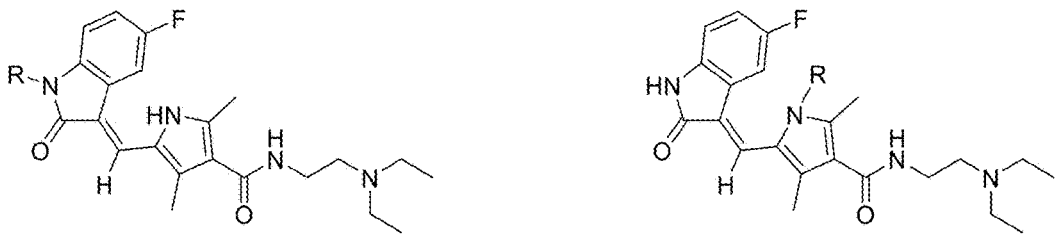


FIG. 5JJ

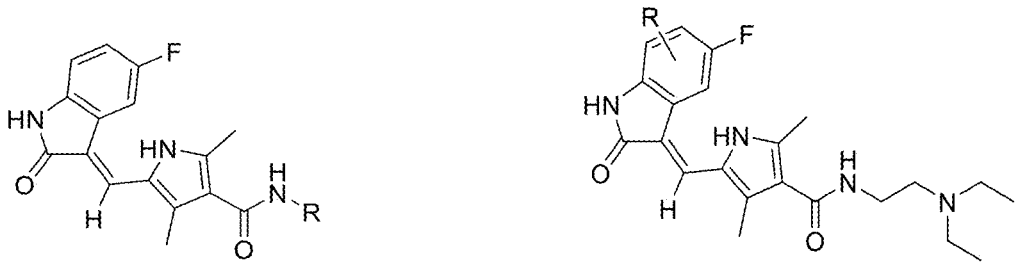


FIG. 5KK

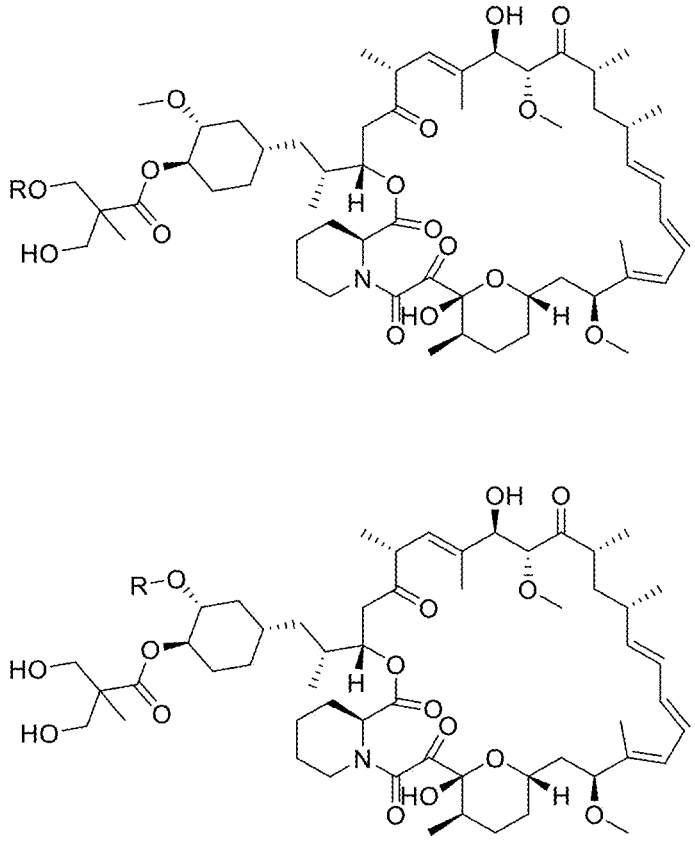


FIG. 5LL

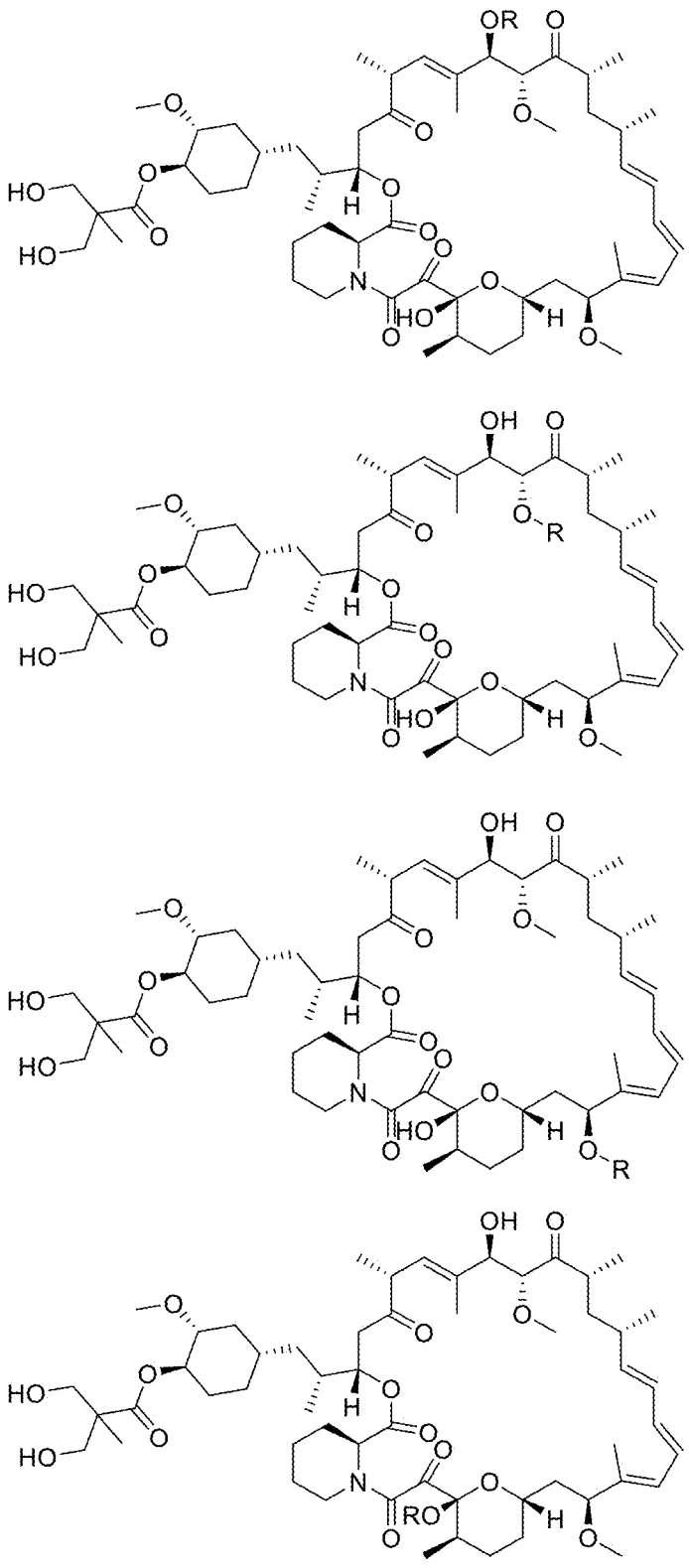


FIG. 5MM

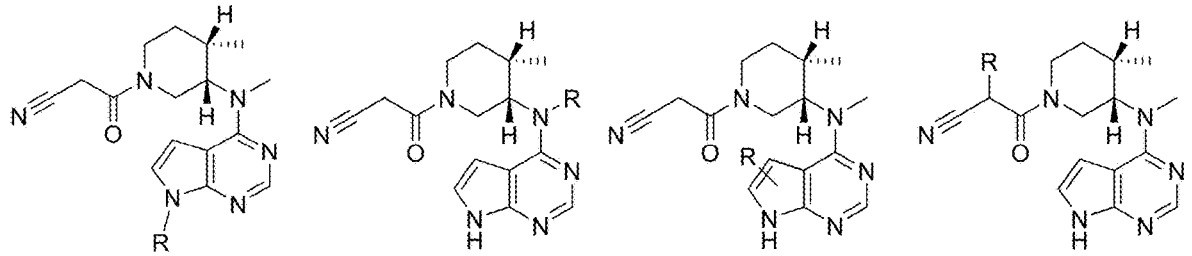


FIG. 5NN

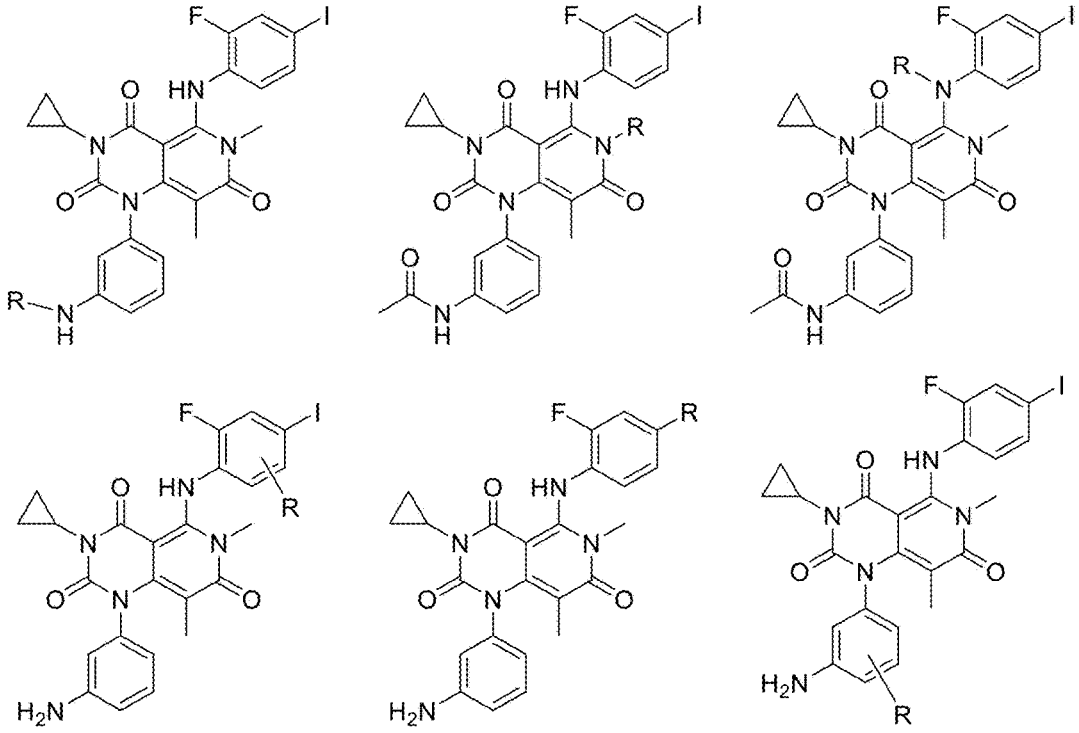


FIG. 5OO

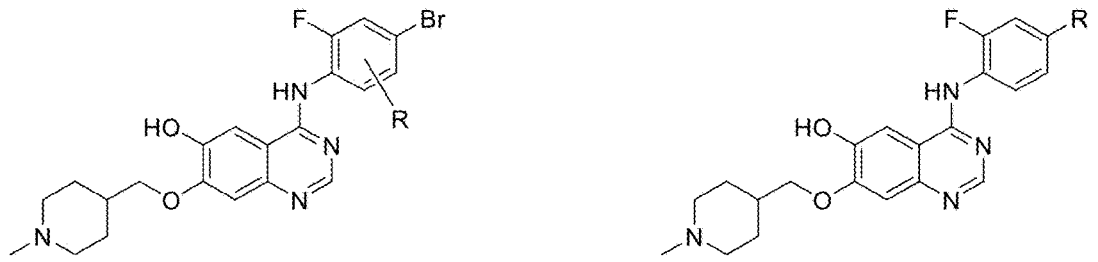


FIG. 5PP

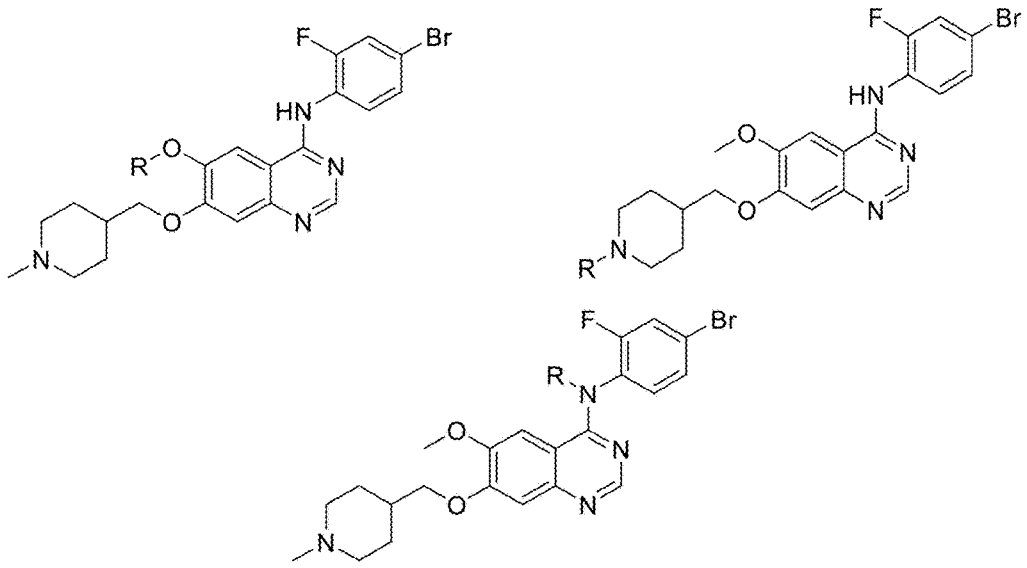


FIG. 5QQ

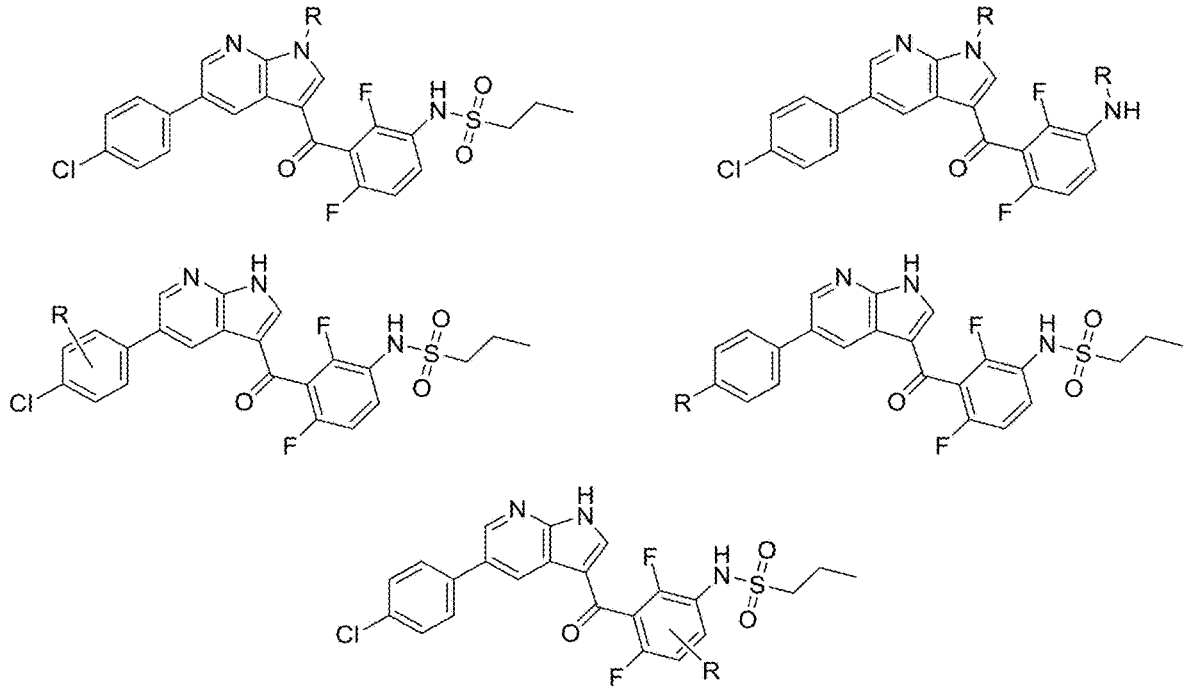


FIG. 5RR

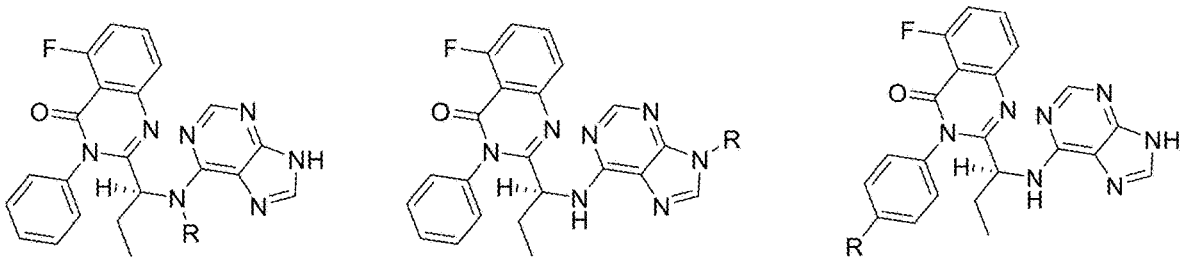


FIG. 5SS

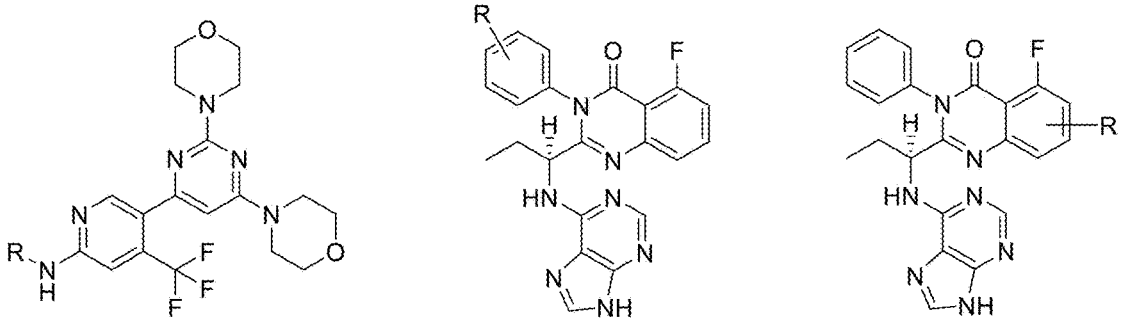


FIG. 5TT

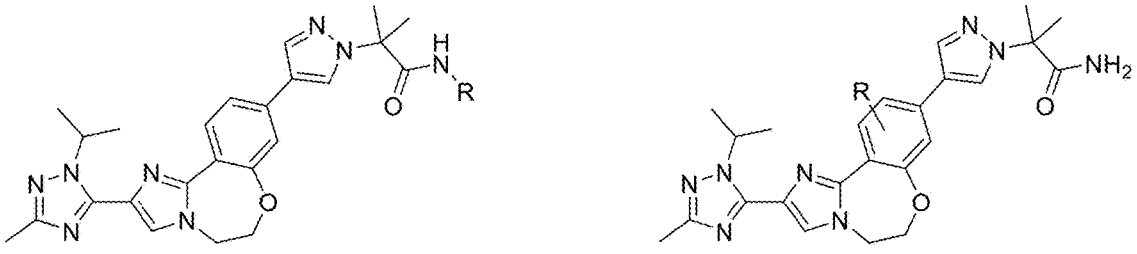


FIG. 5UU

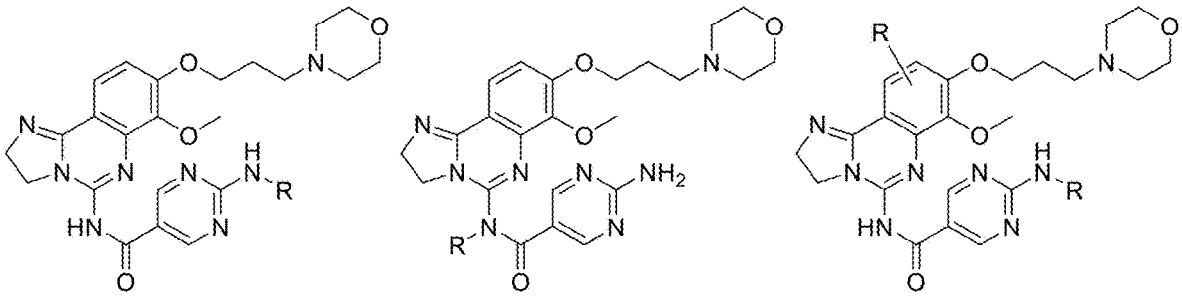


FIG. 5VV

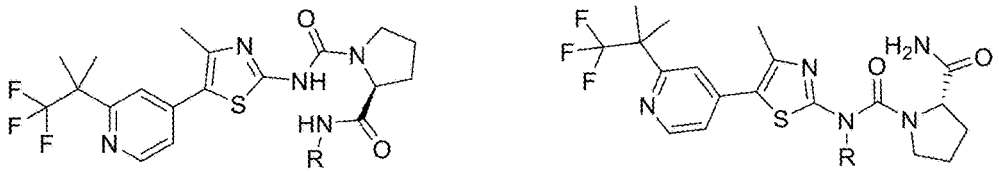


FIG. 5WW

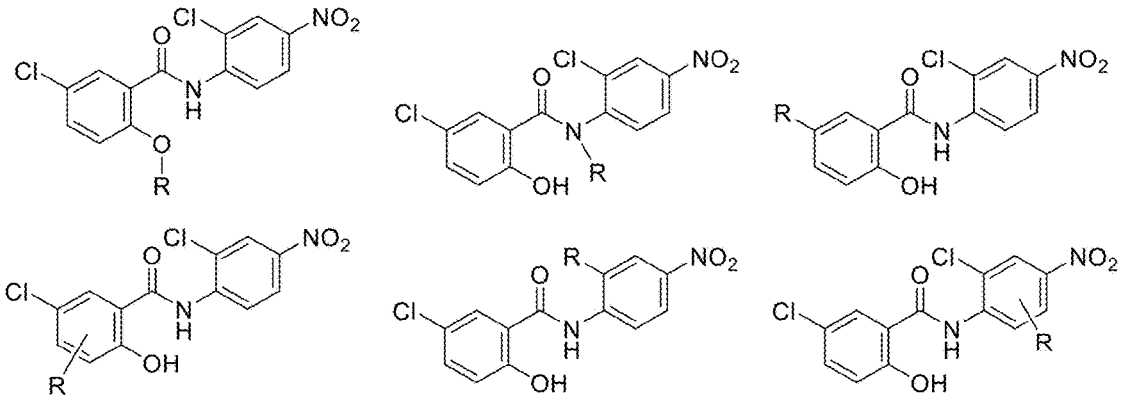


FIG. 6A

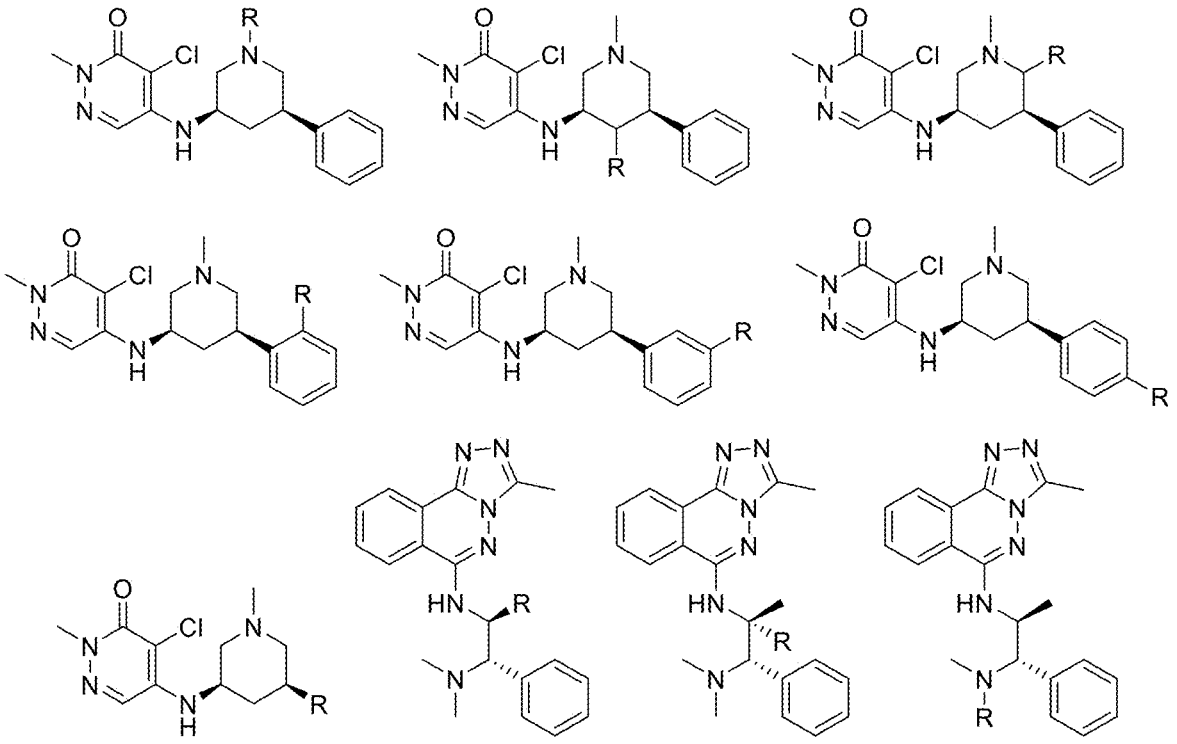


FIG. 6B

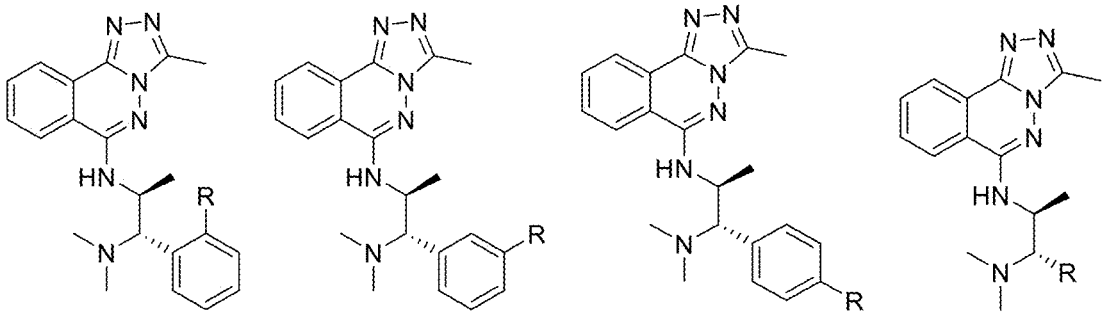


FIG. 6C

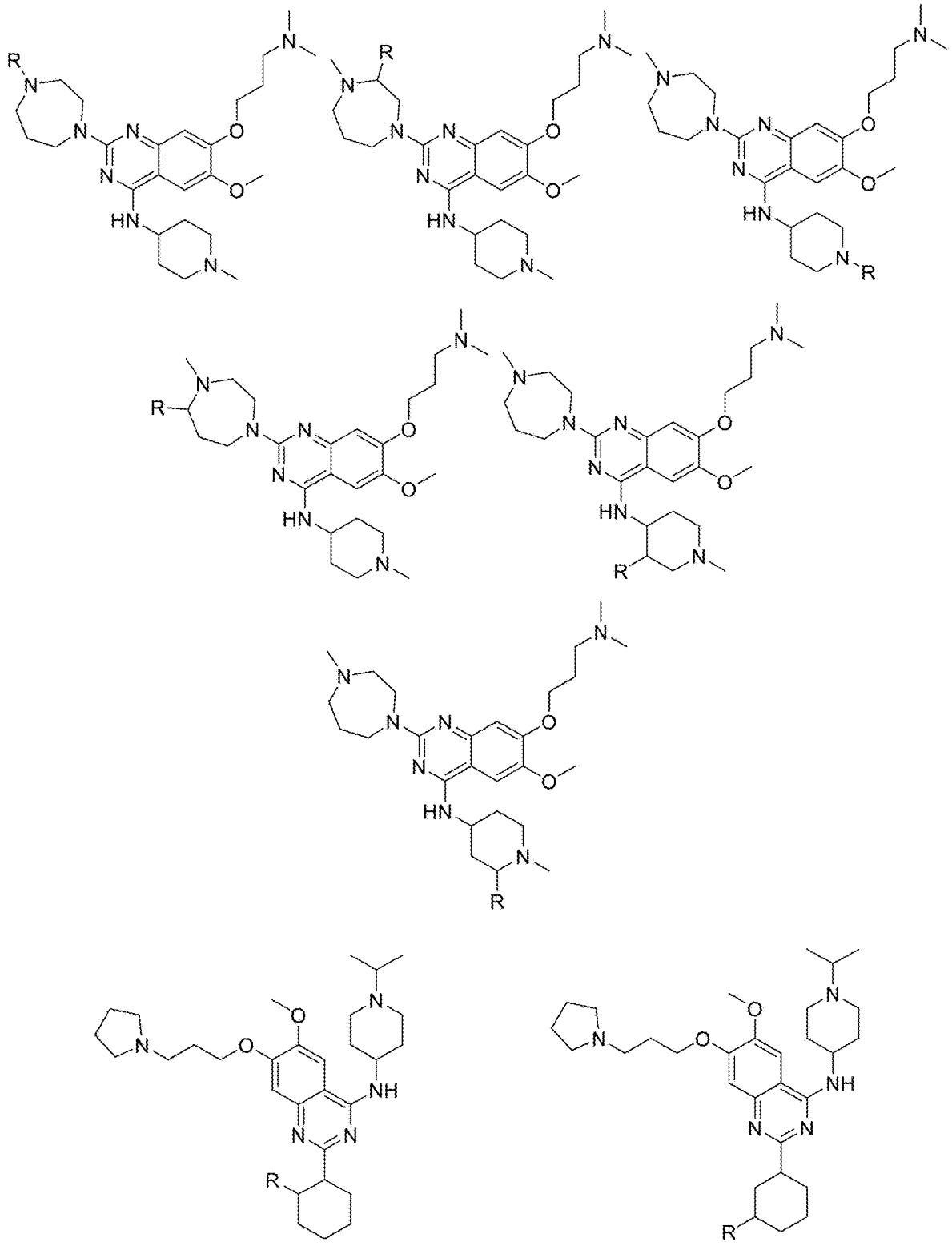


FIG. 6D

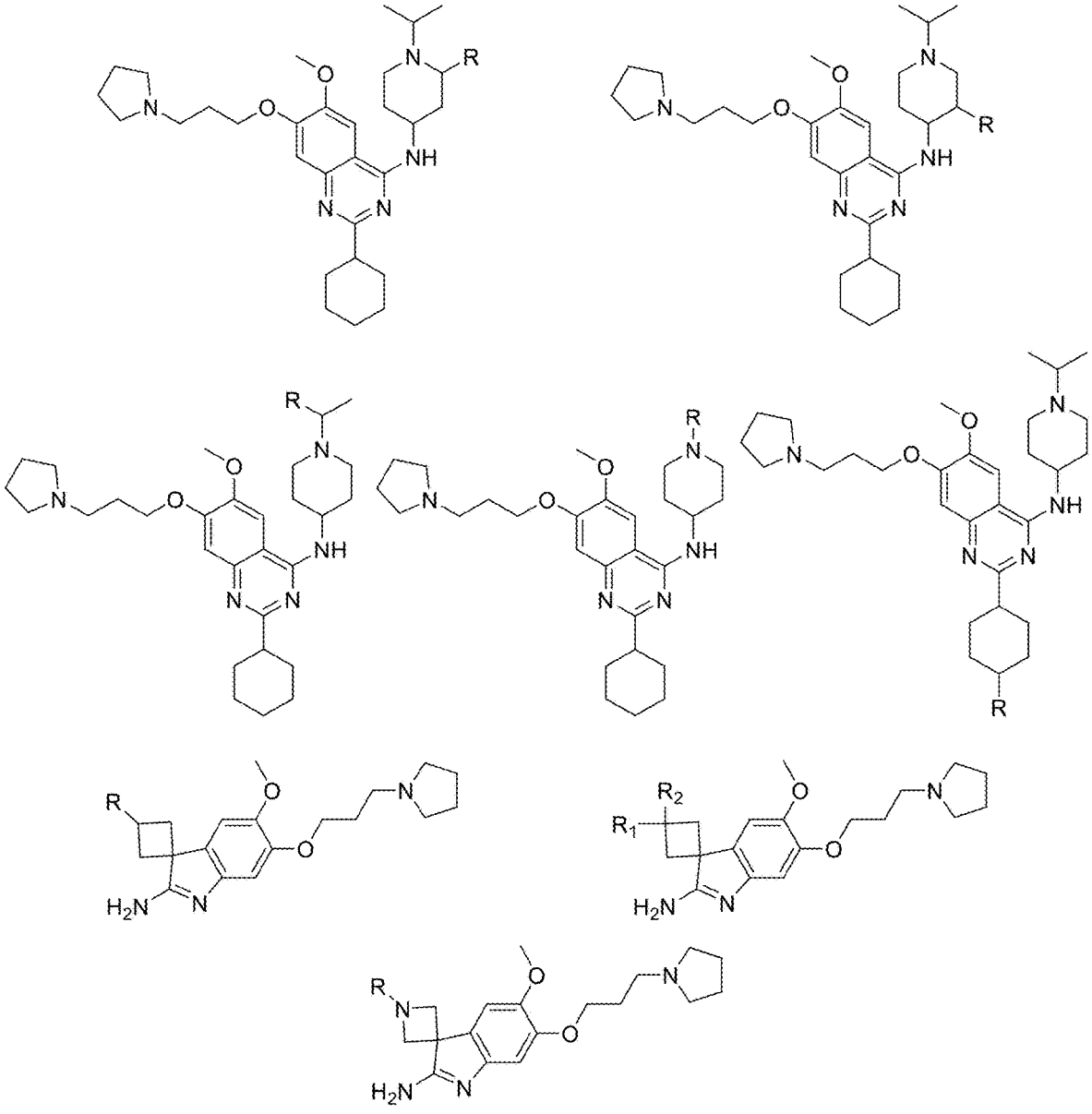


FIG. 6E

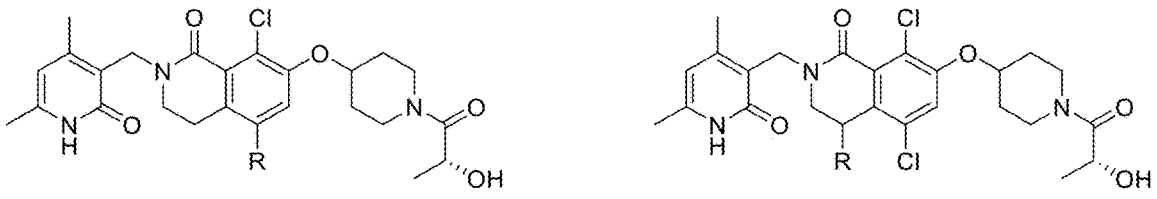


FIG. 6F

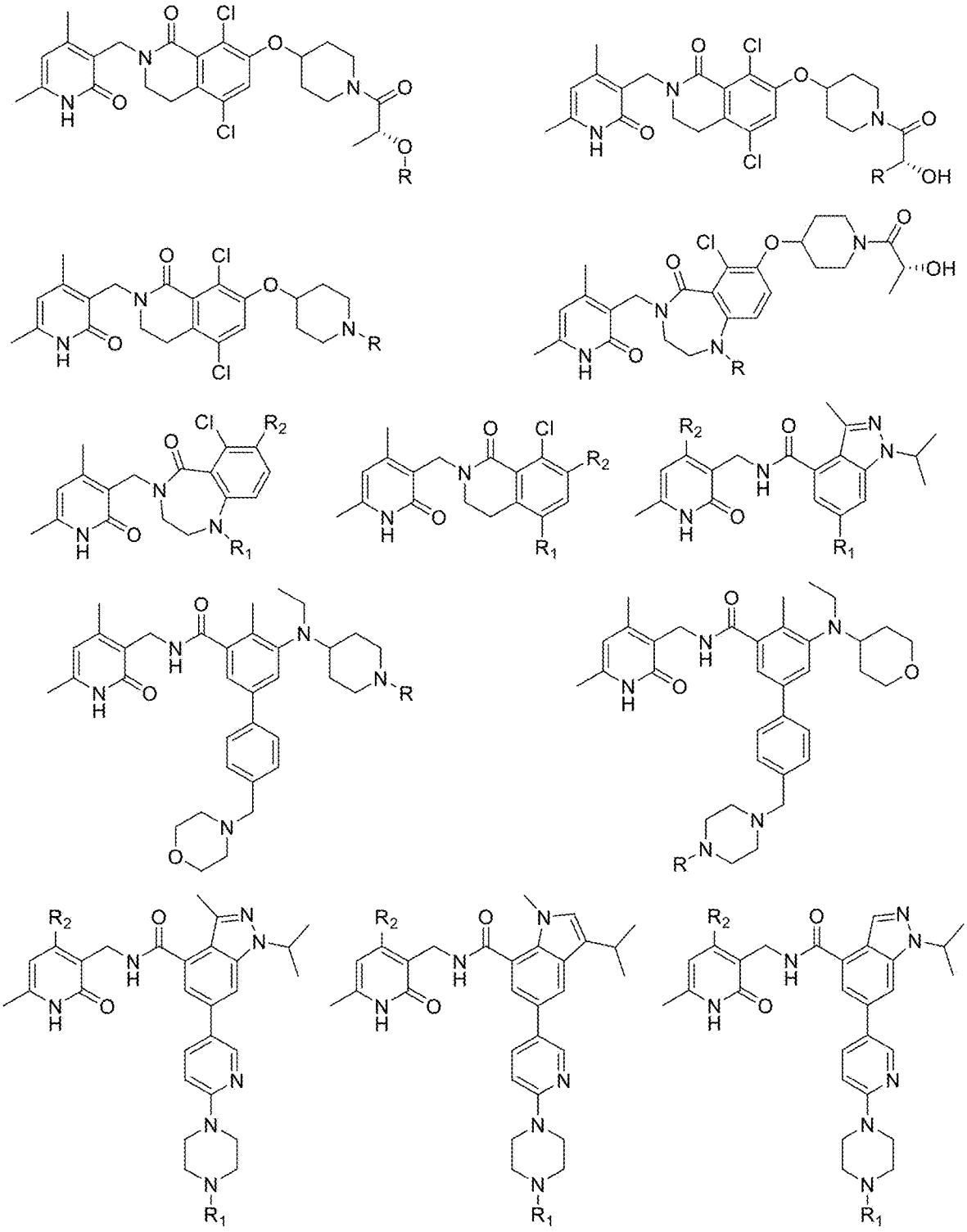


FIG. 6G

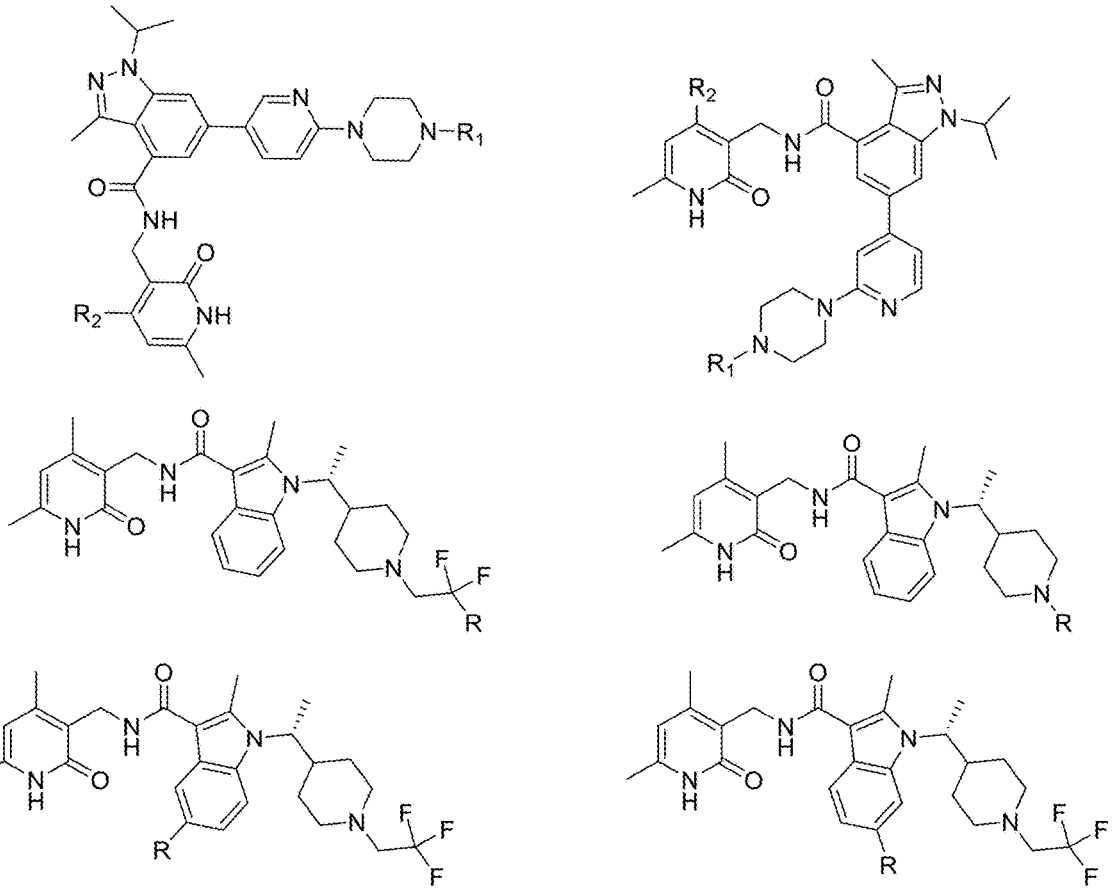


FIG. 6H

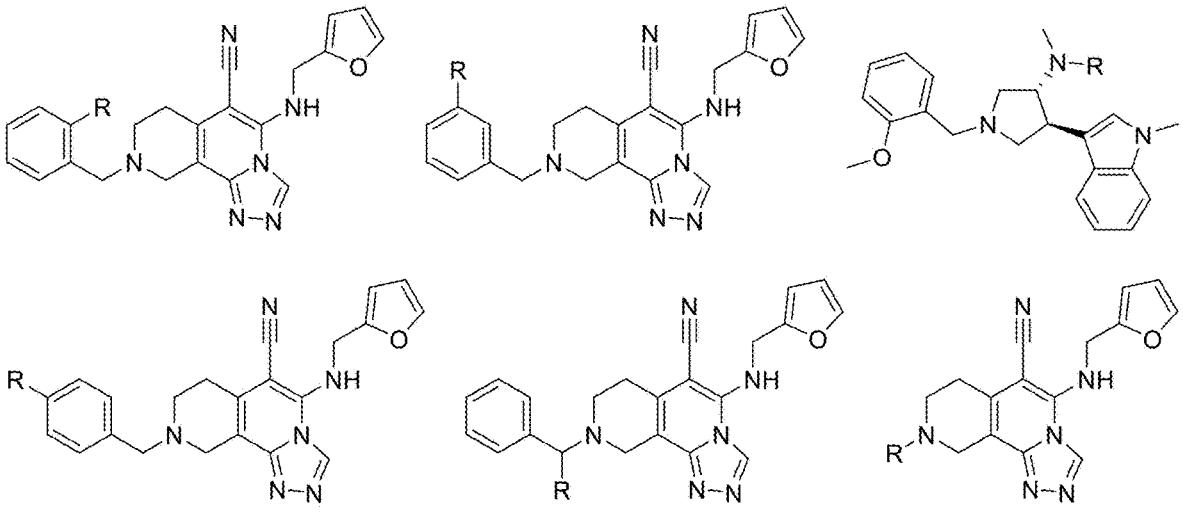


FIG. 6I

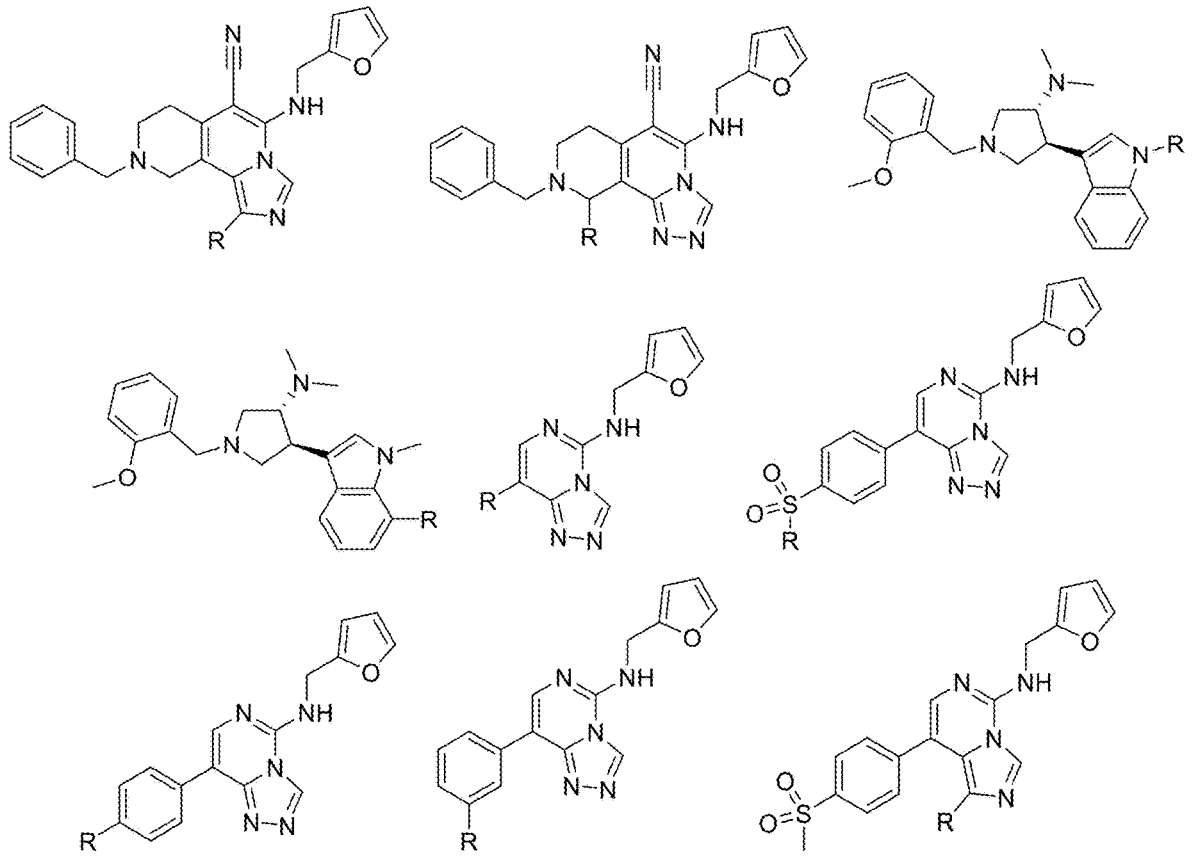


FIG. 6J

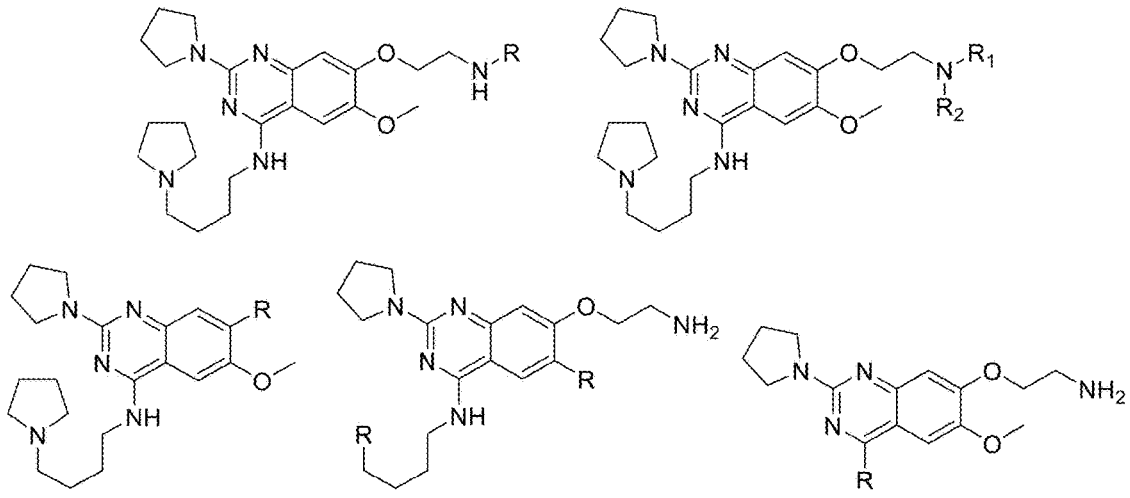
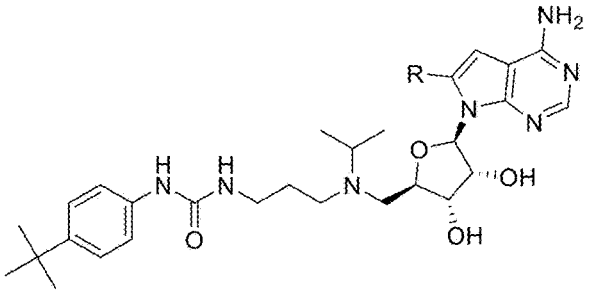
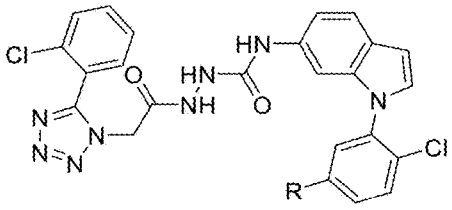
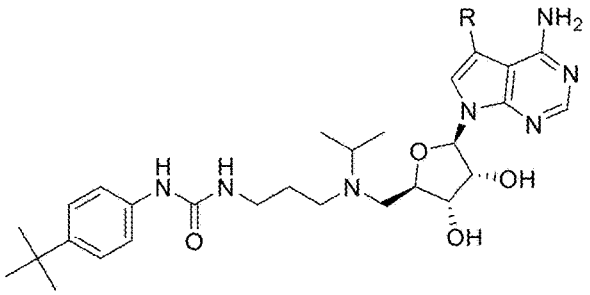
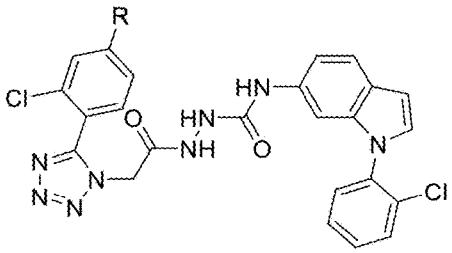


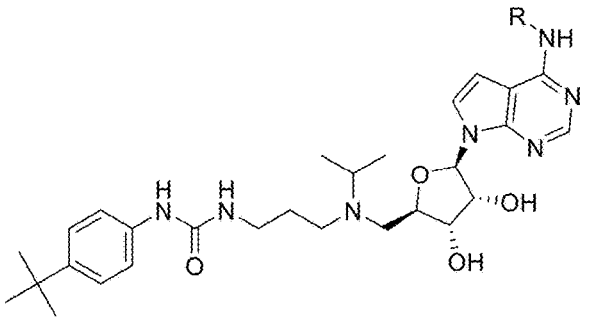
FIG. 6K

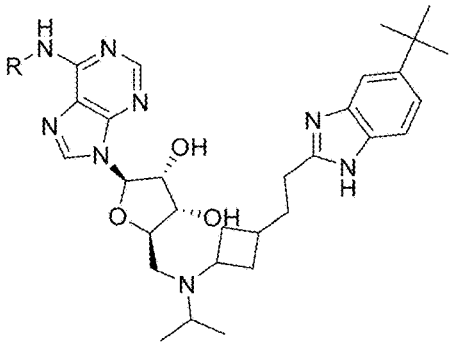


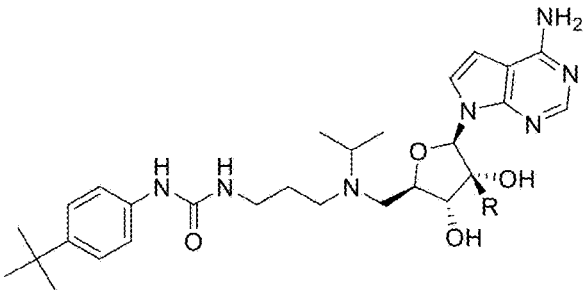












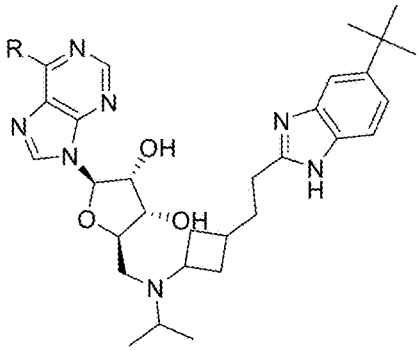


FIG. 6L

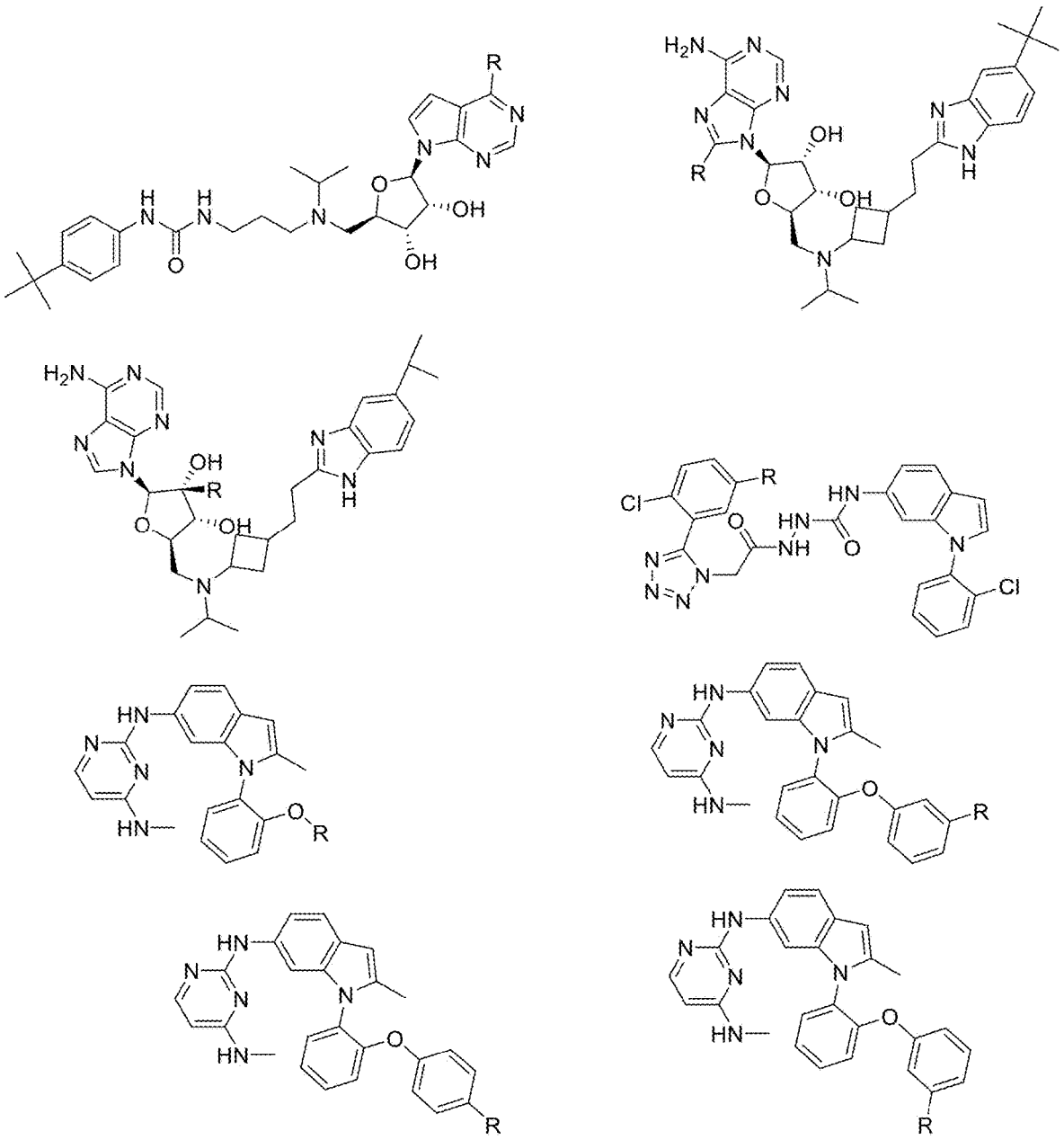


FIG. 6M

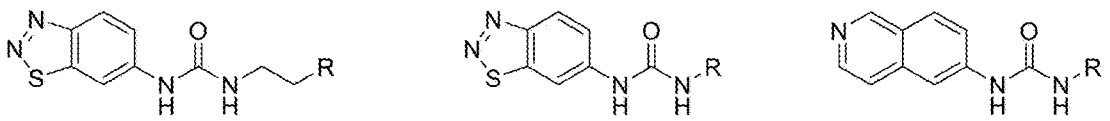


FIG. 6N

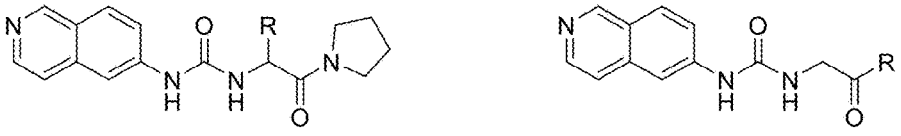


FIG. 6O

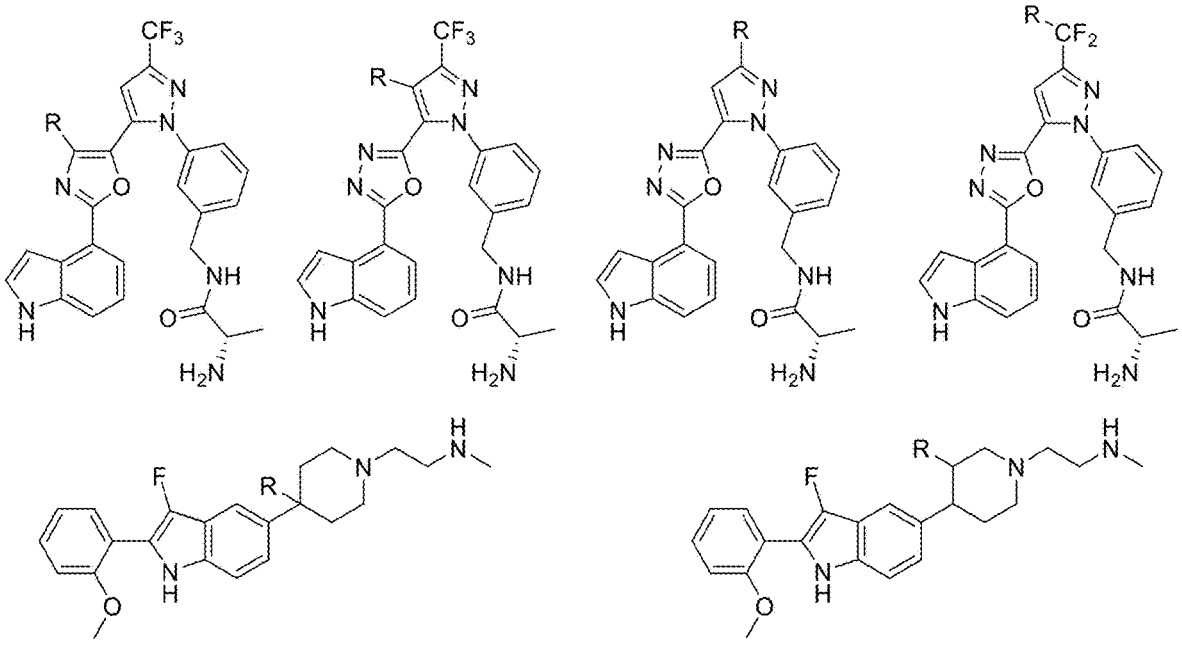


FIG. 6P

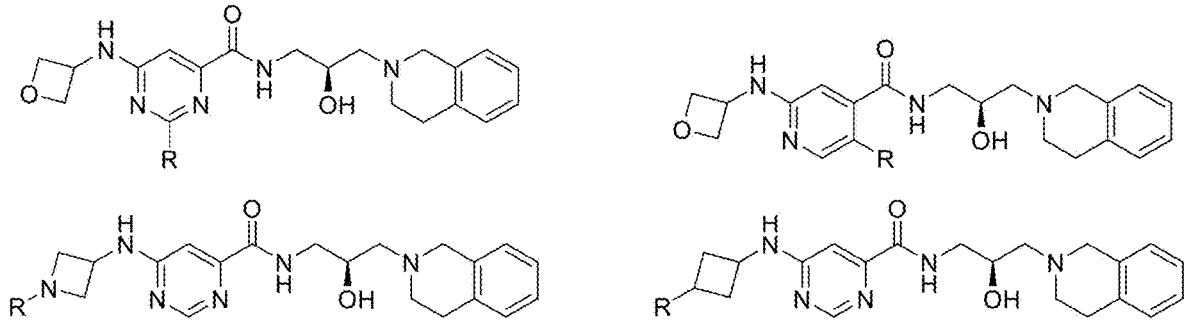


FIG. 6Q

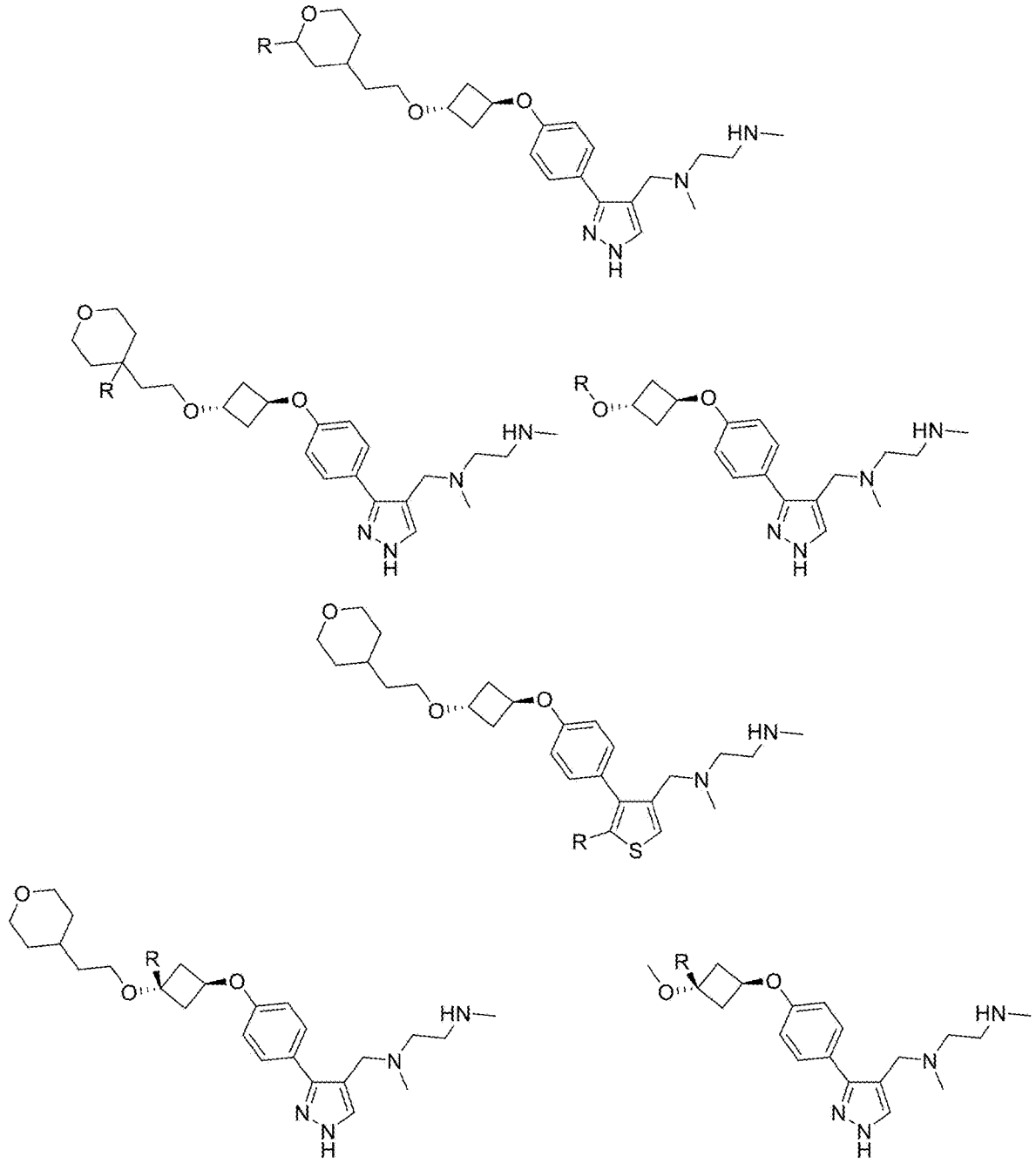


FIG. 6R

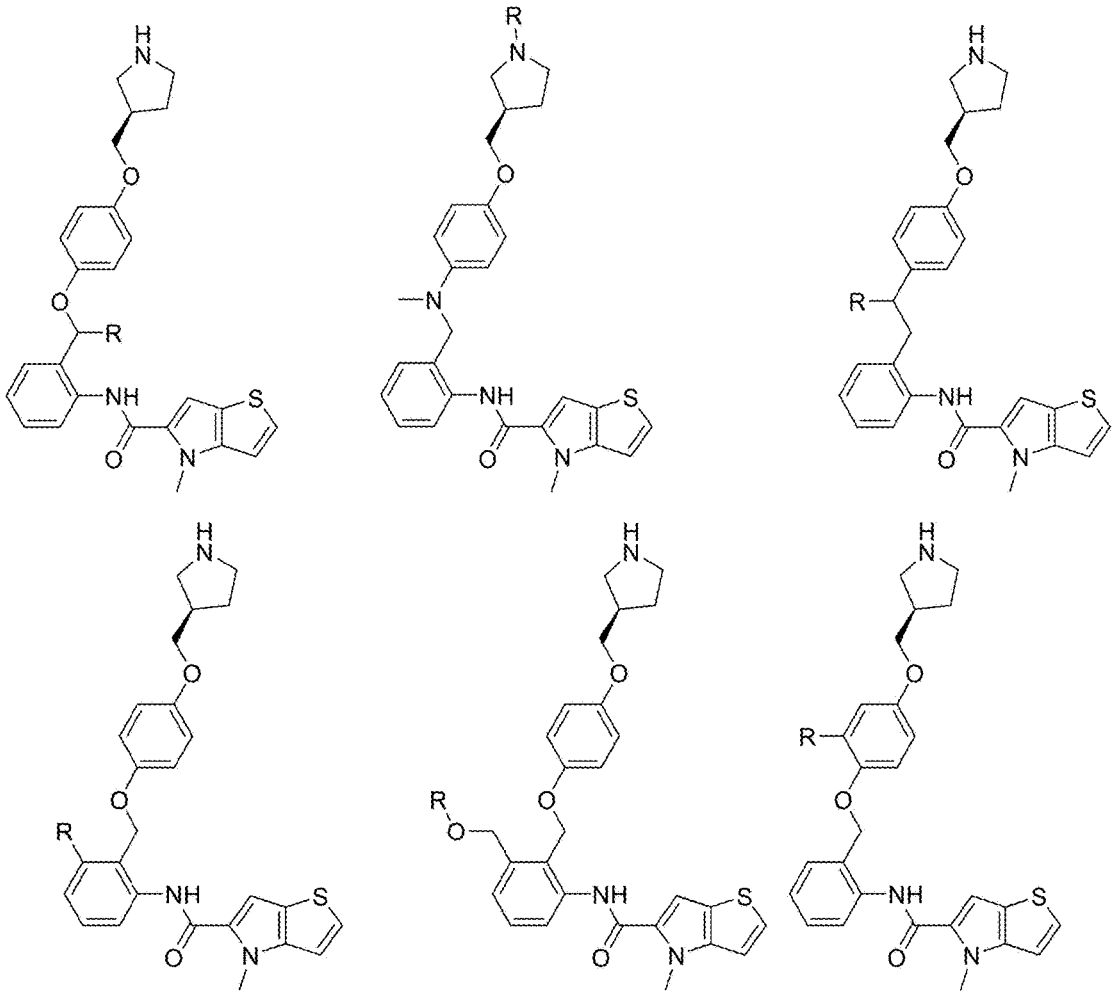


FIG. 6S

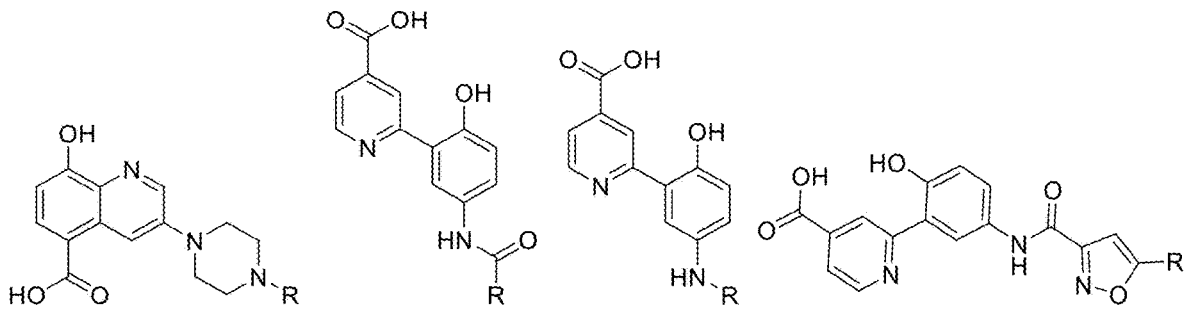


FIG. 6T

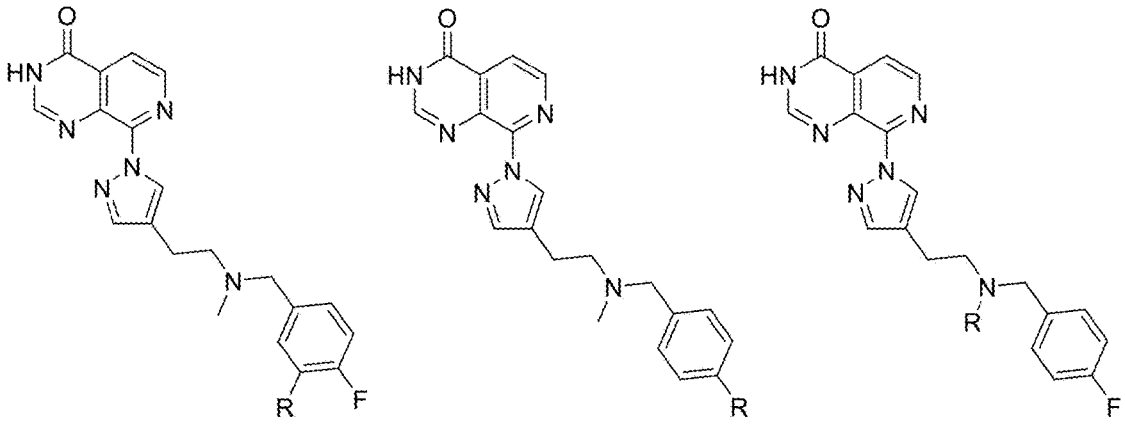


FIG. 6U

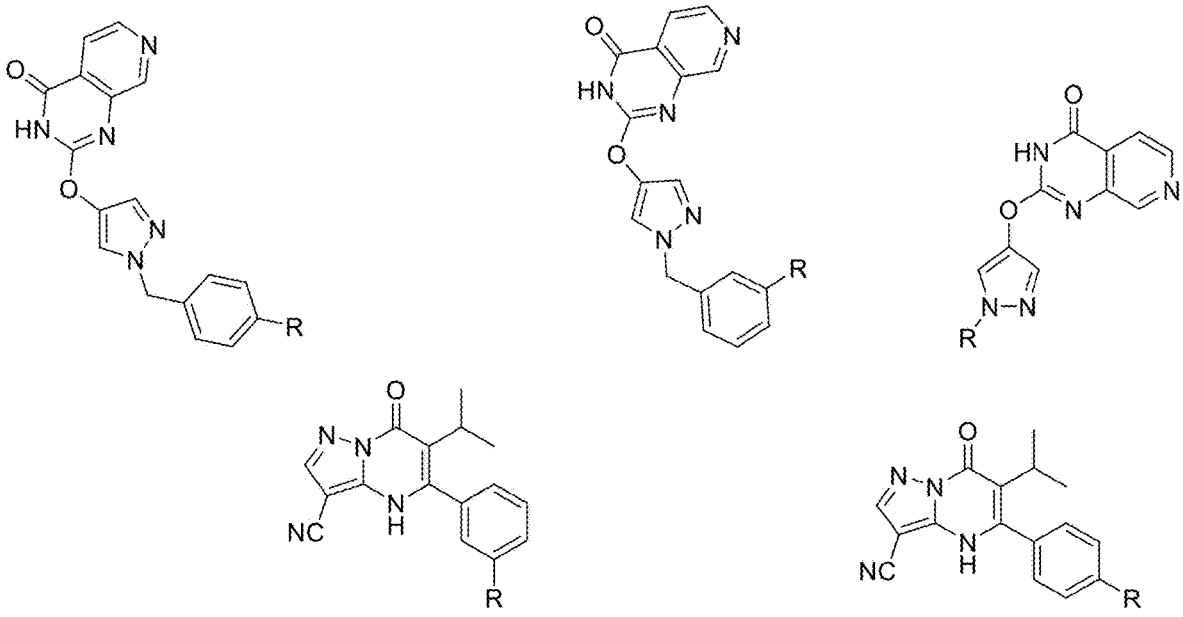


FIG. 6V

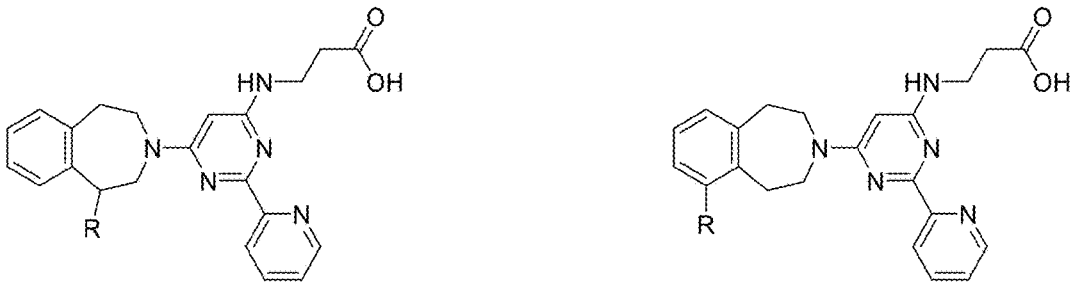


FIG. 6W

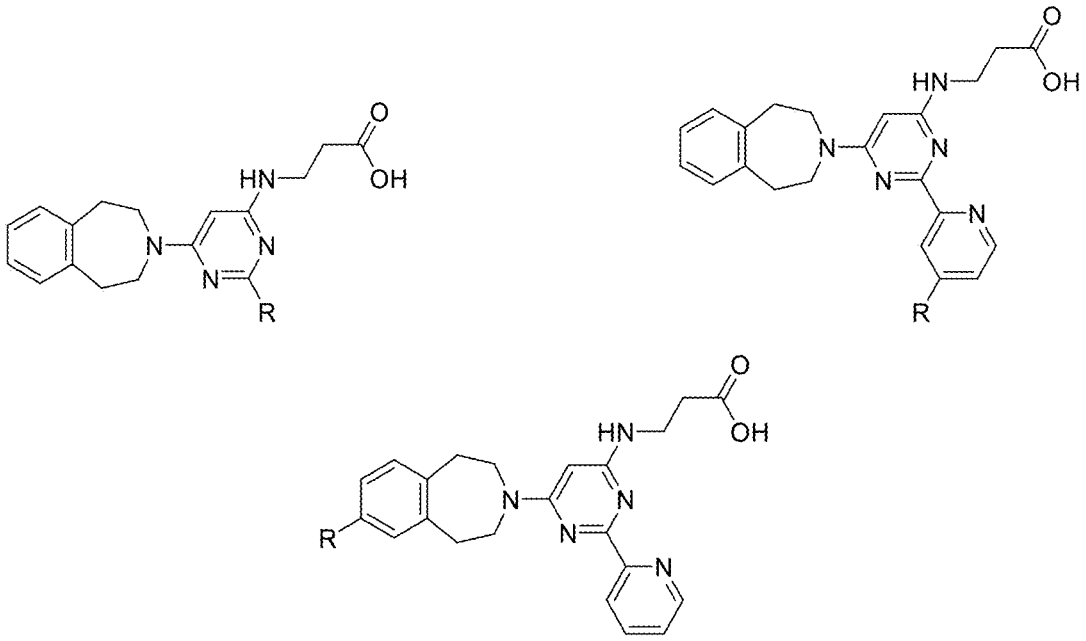

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FIG. 6X

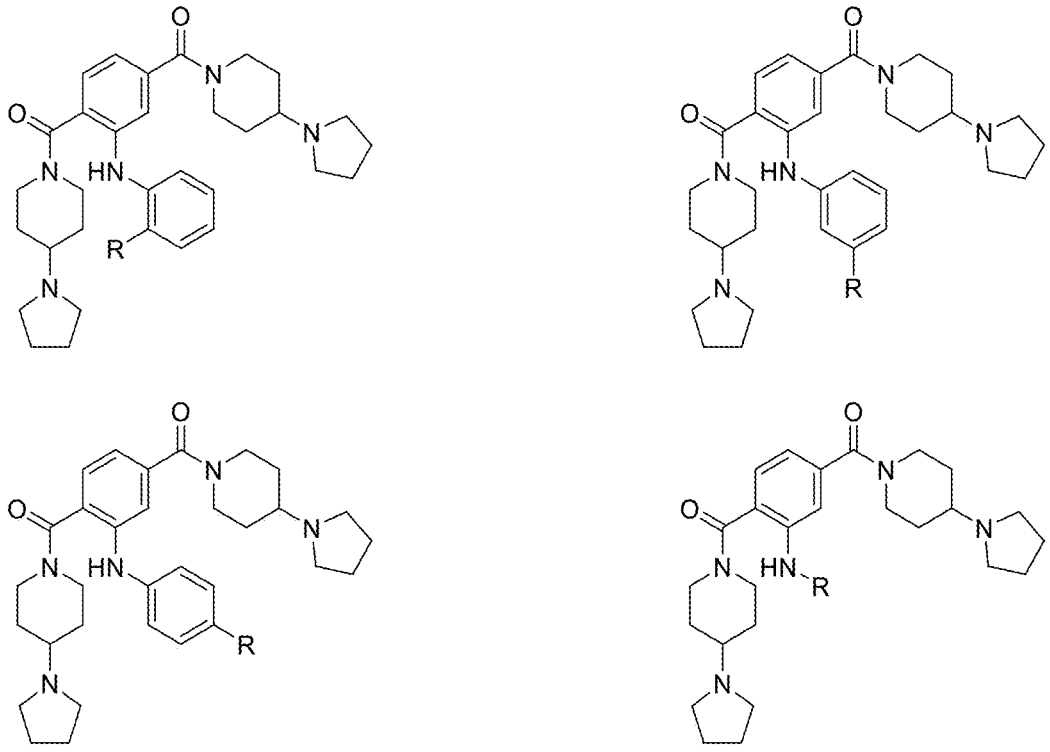
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FIG. 6Y

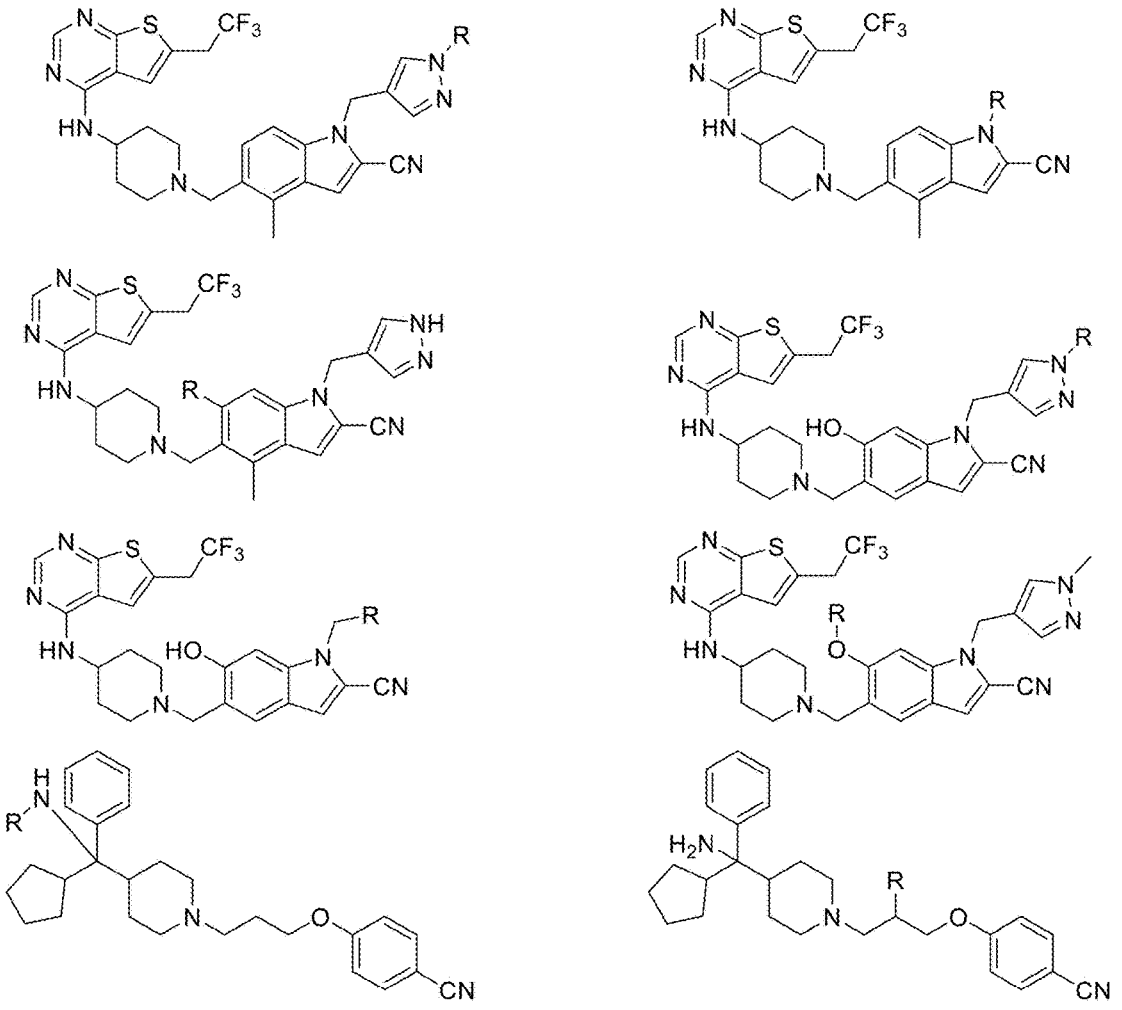


FIG. 6Z

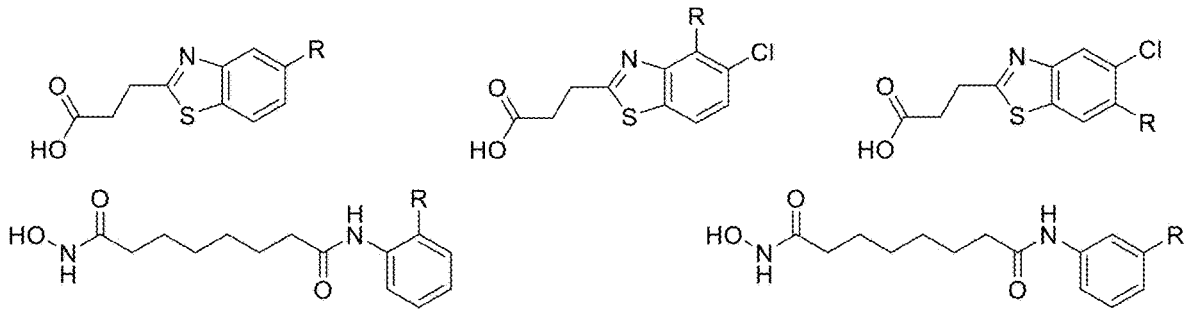


FIG. 6AA

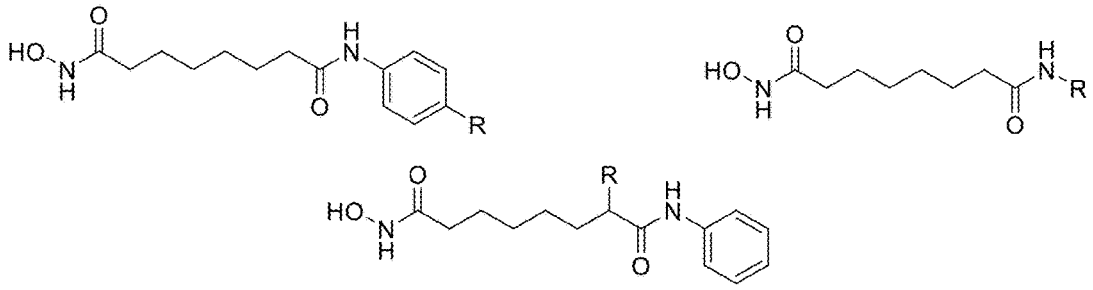
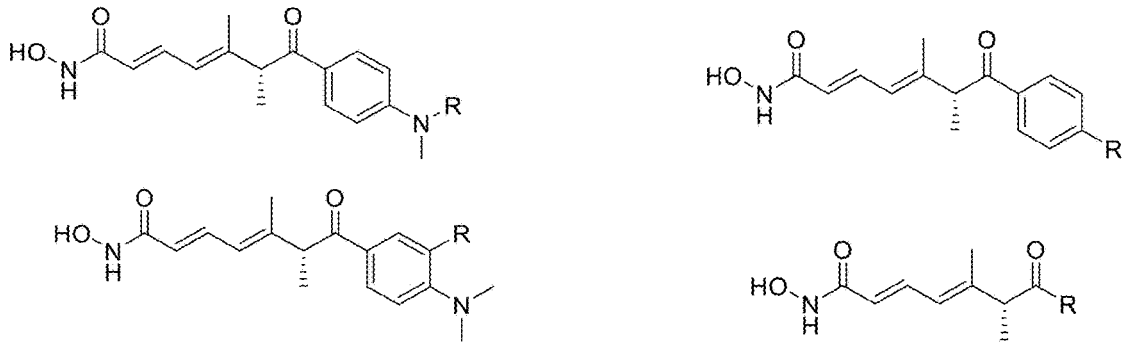


FIG. 6BB



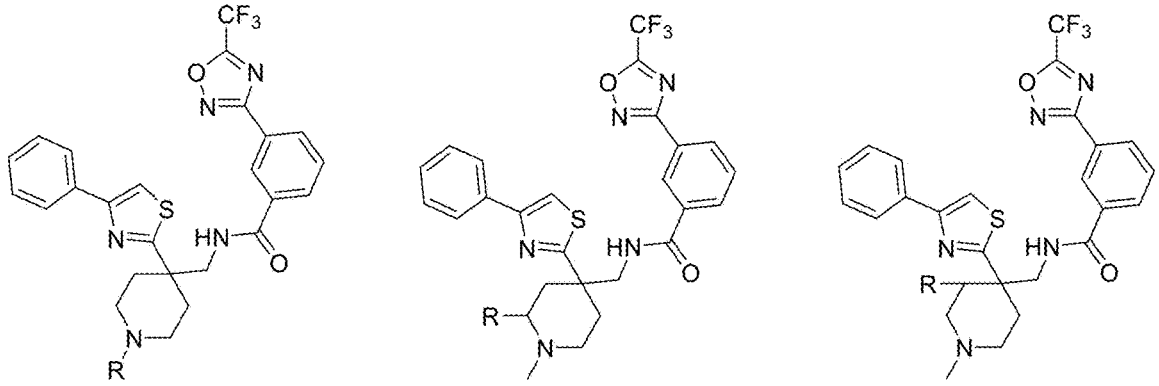


FIG. 7A

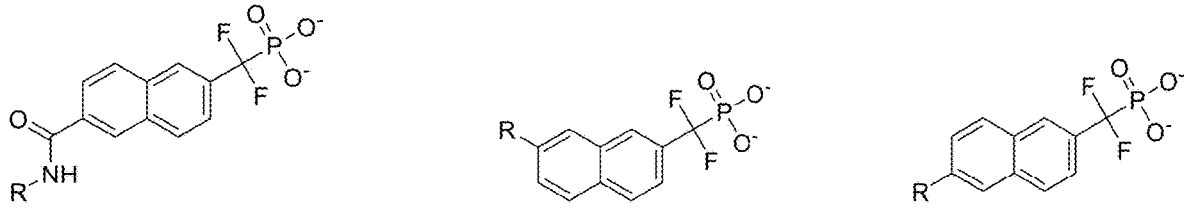


FIG. 7B

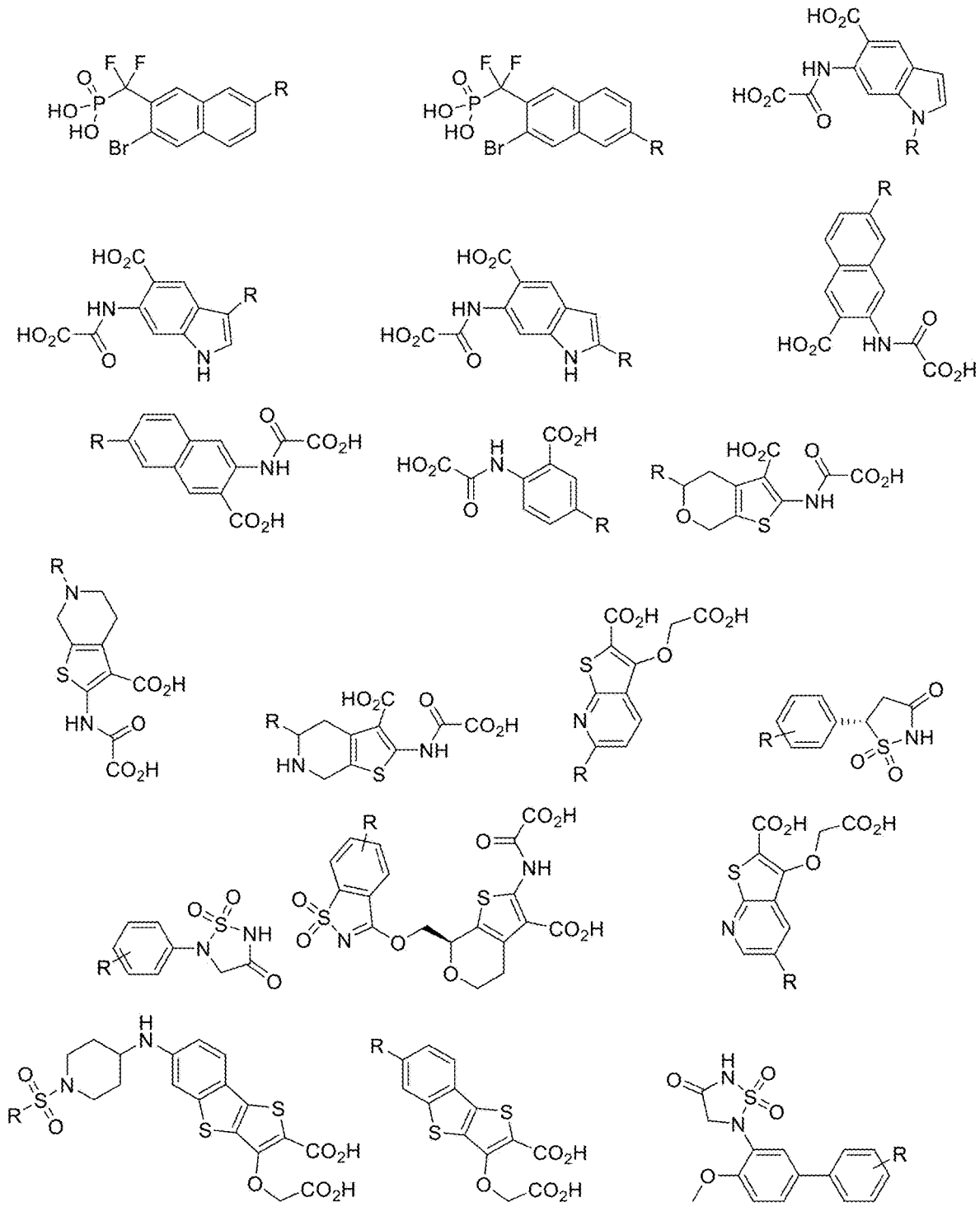


FIG. 7C

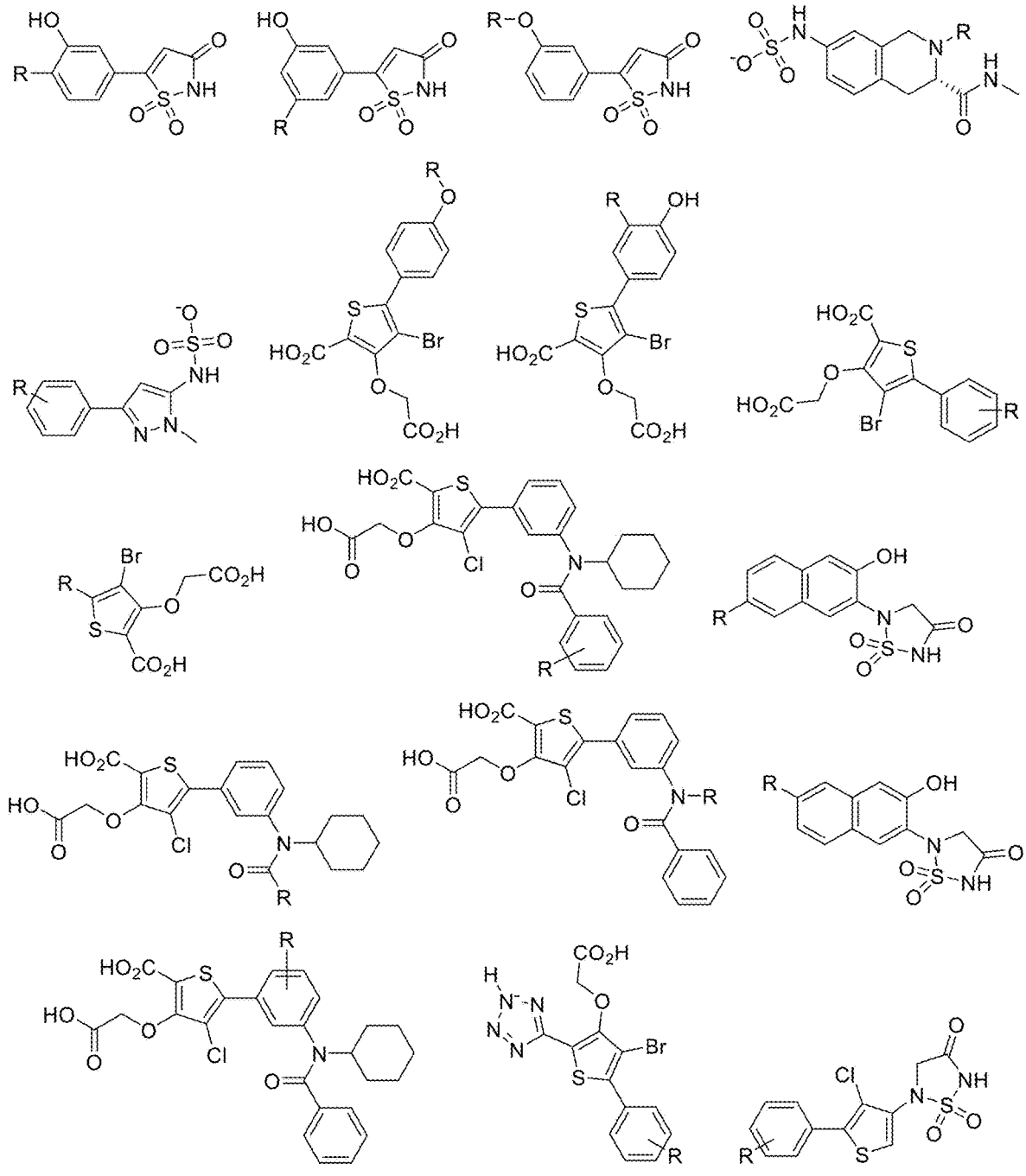


FIG. 7D

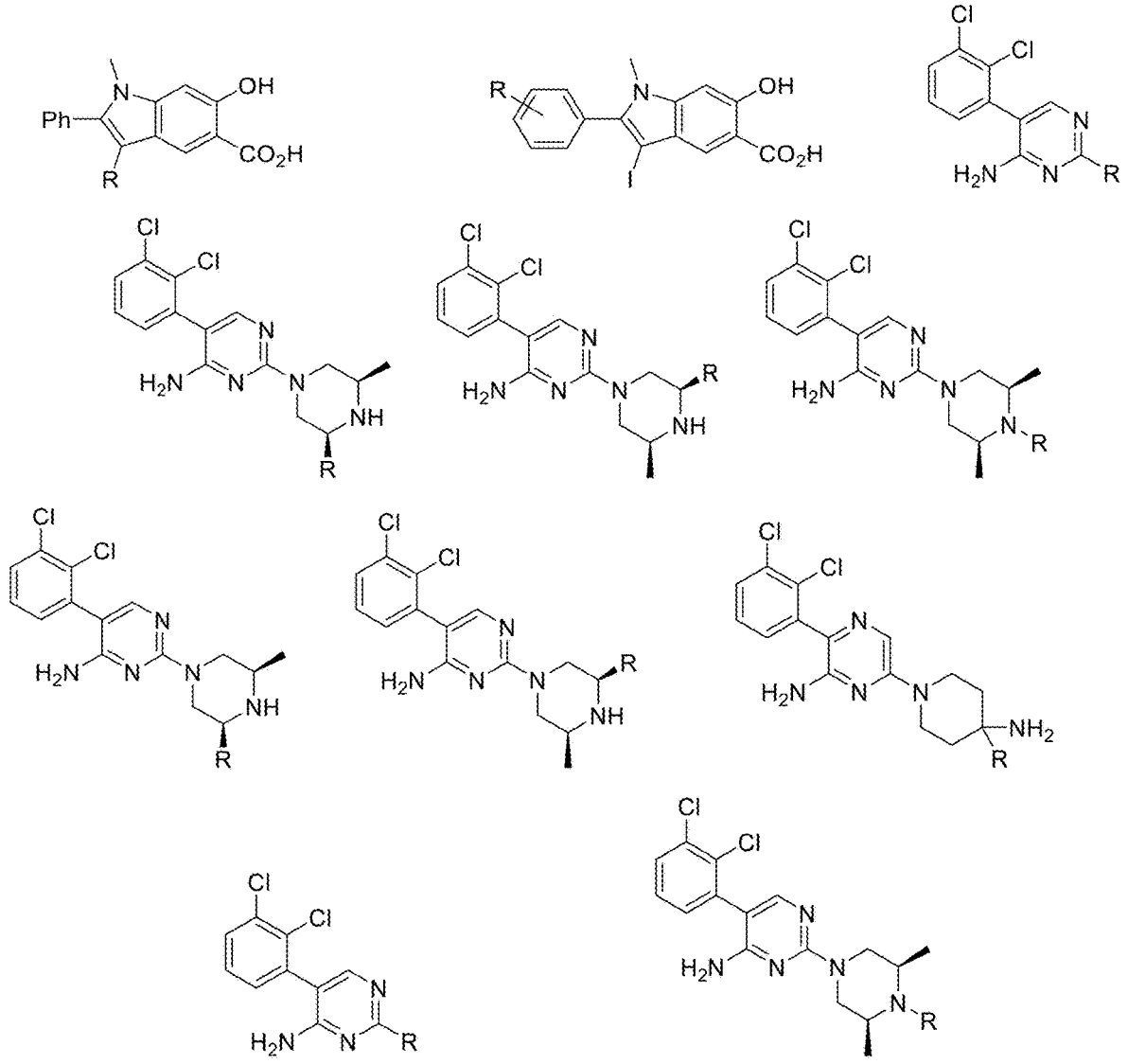


FIG. 7E

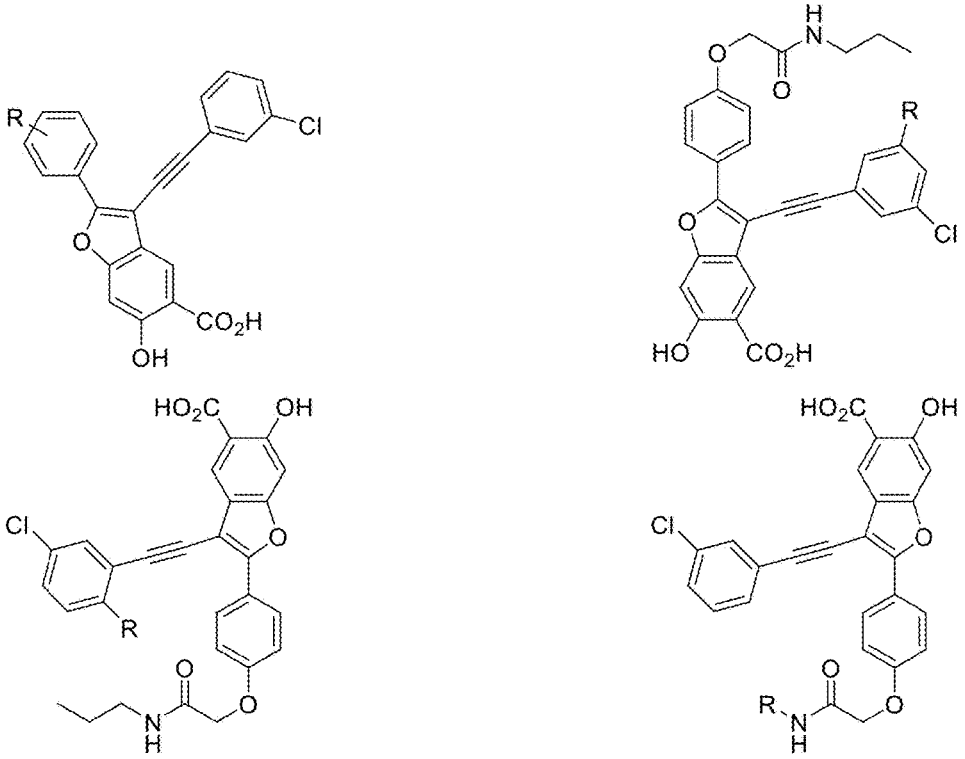


FIG 7F

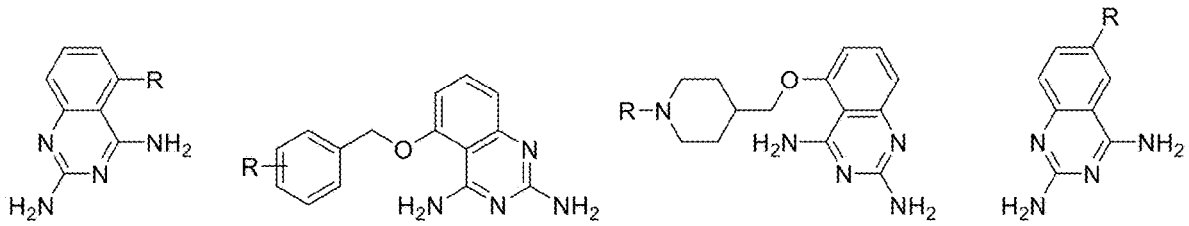


FIG. 8A

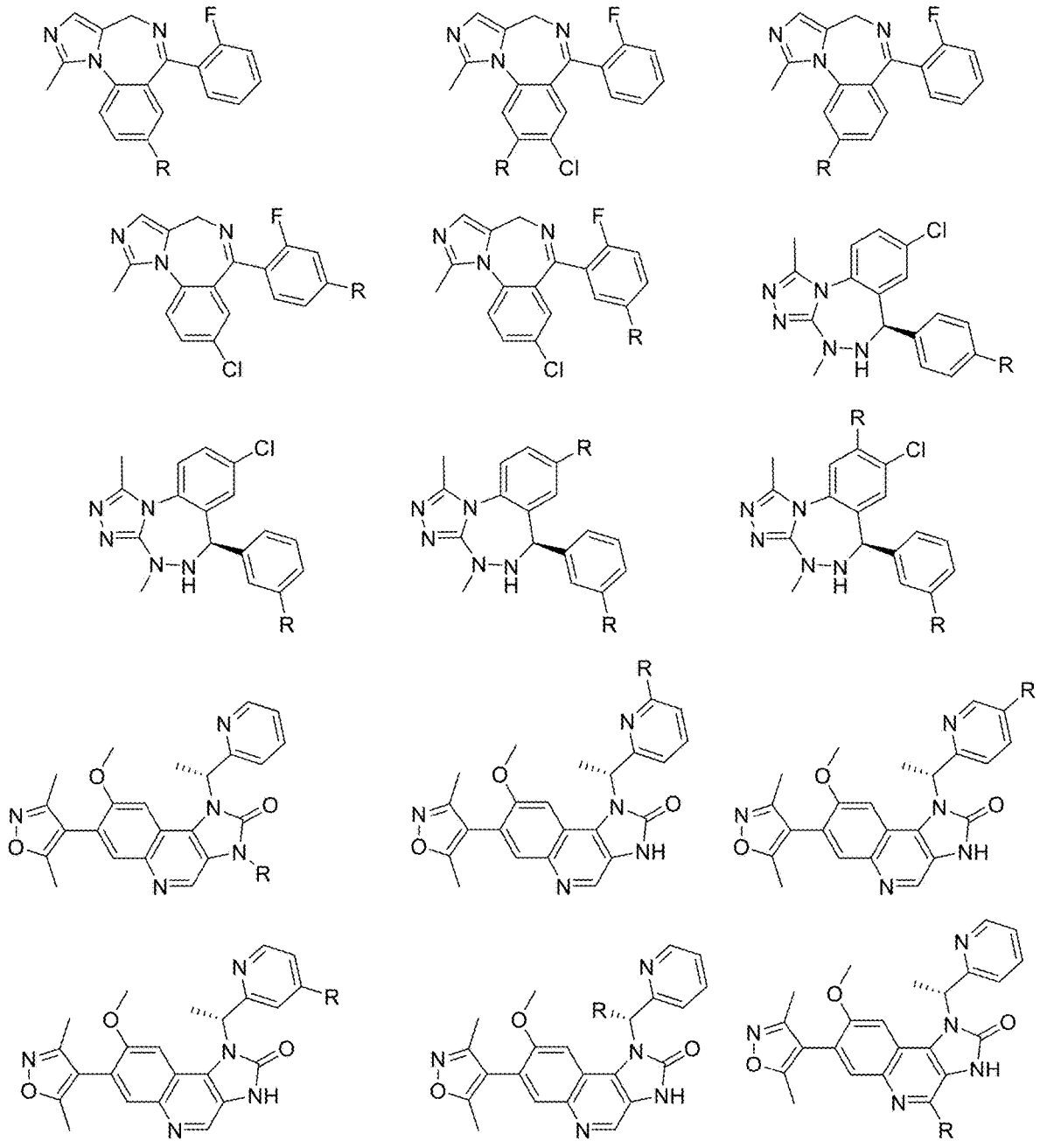


FIG. 8B

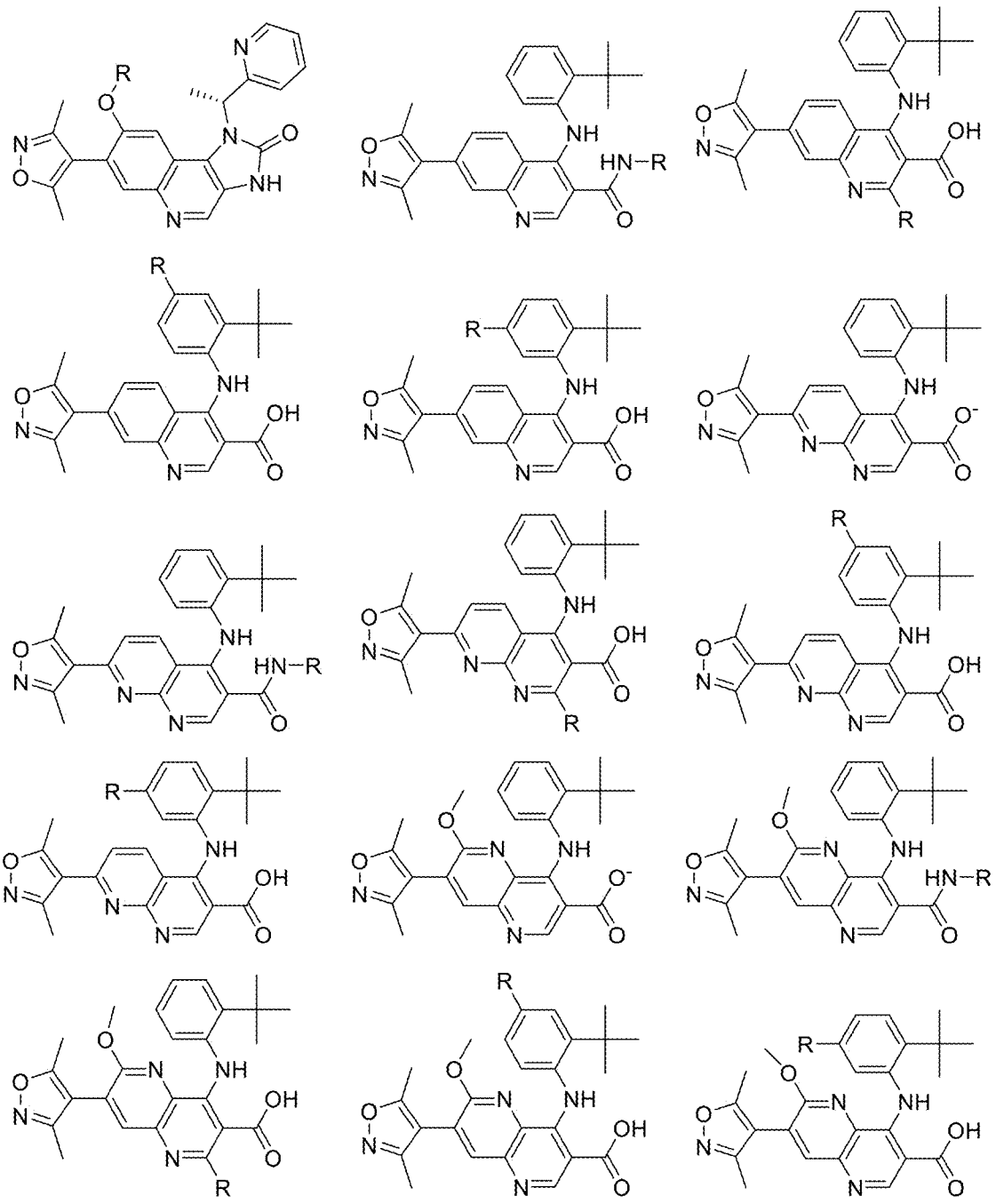


FIG. 8C

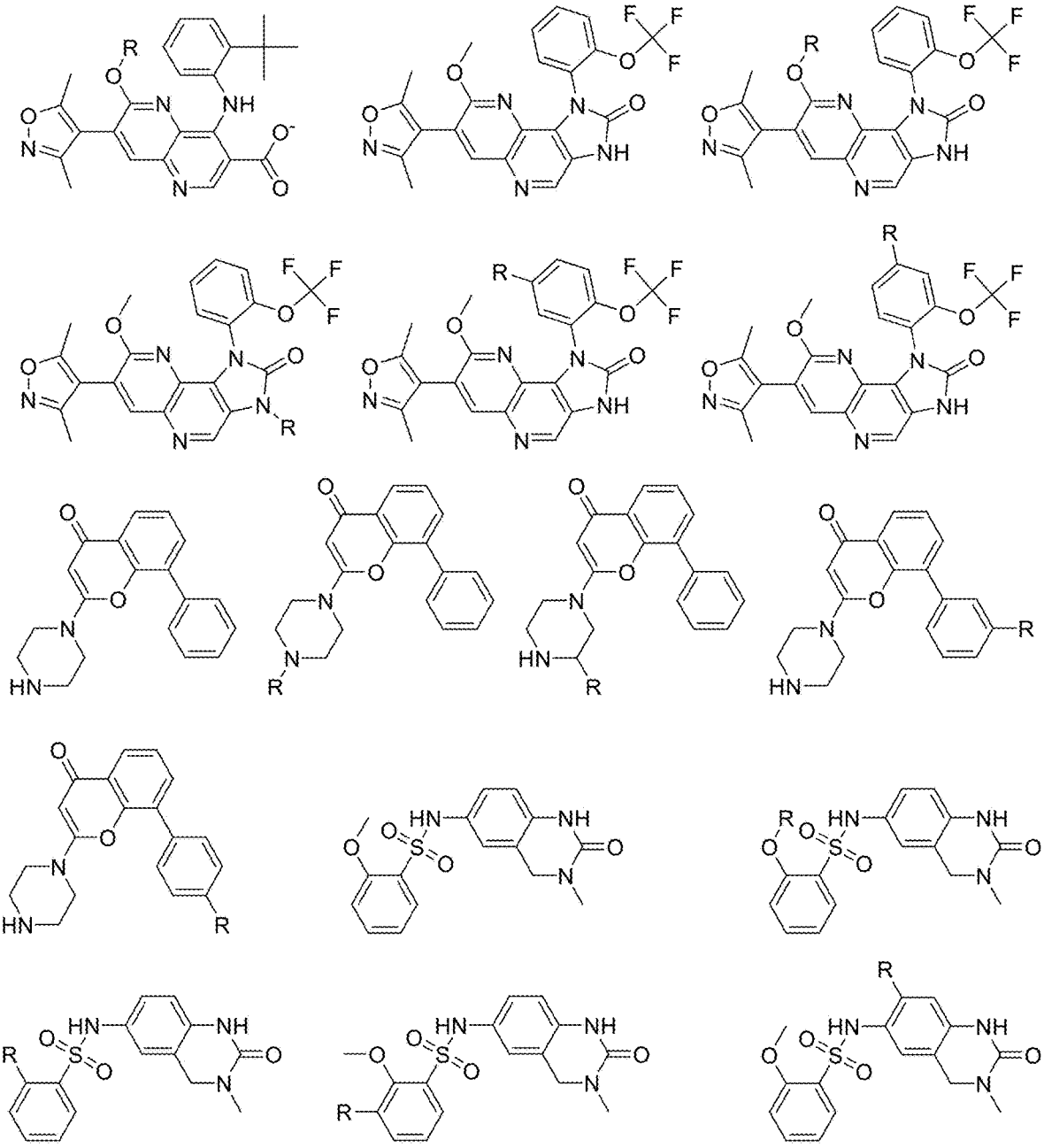


FIG. 8D

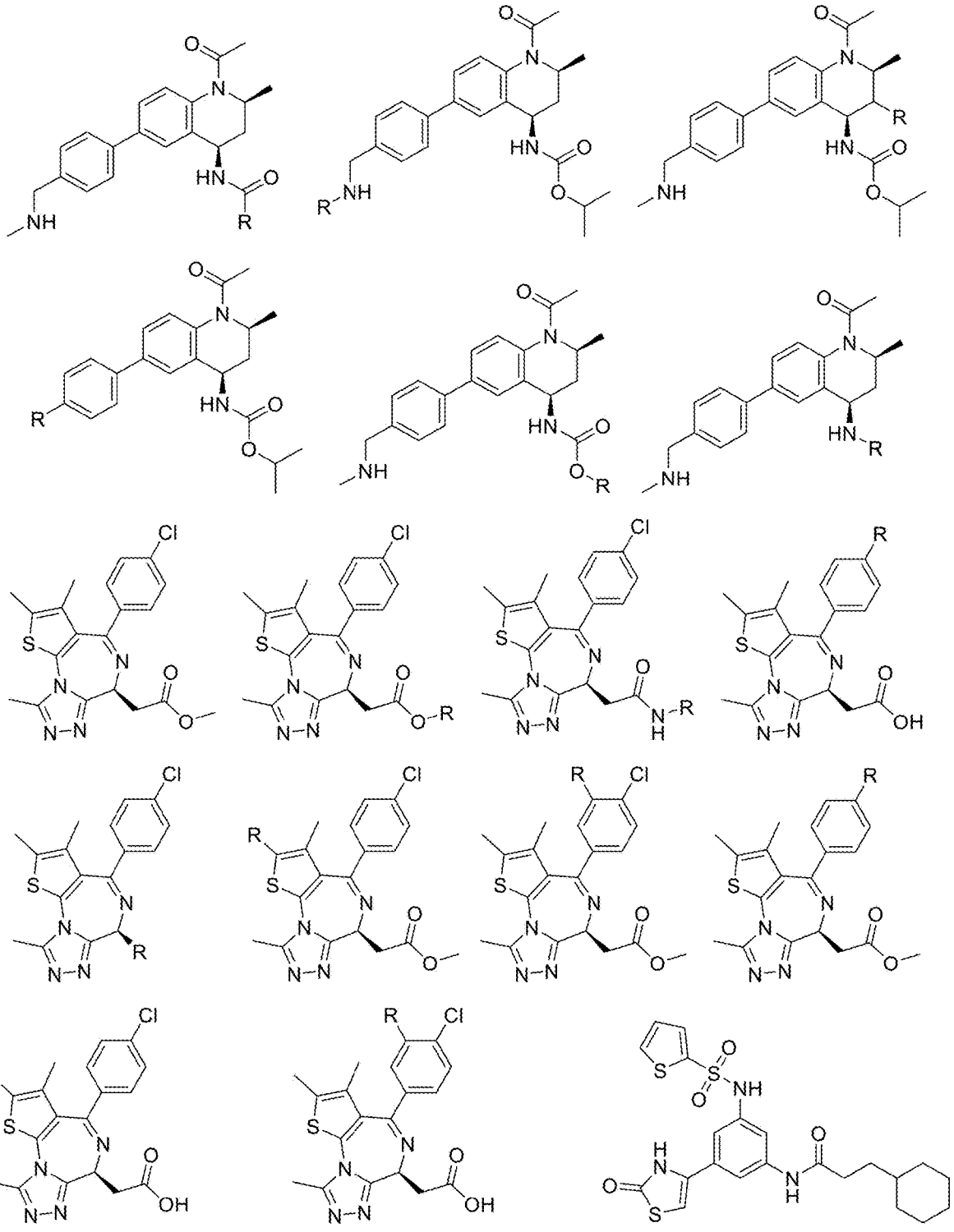


FIG. 8E

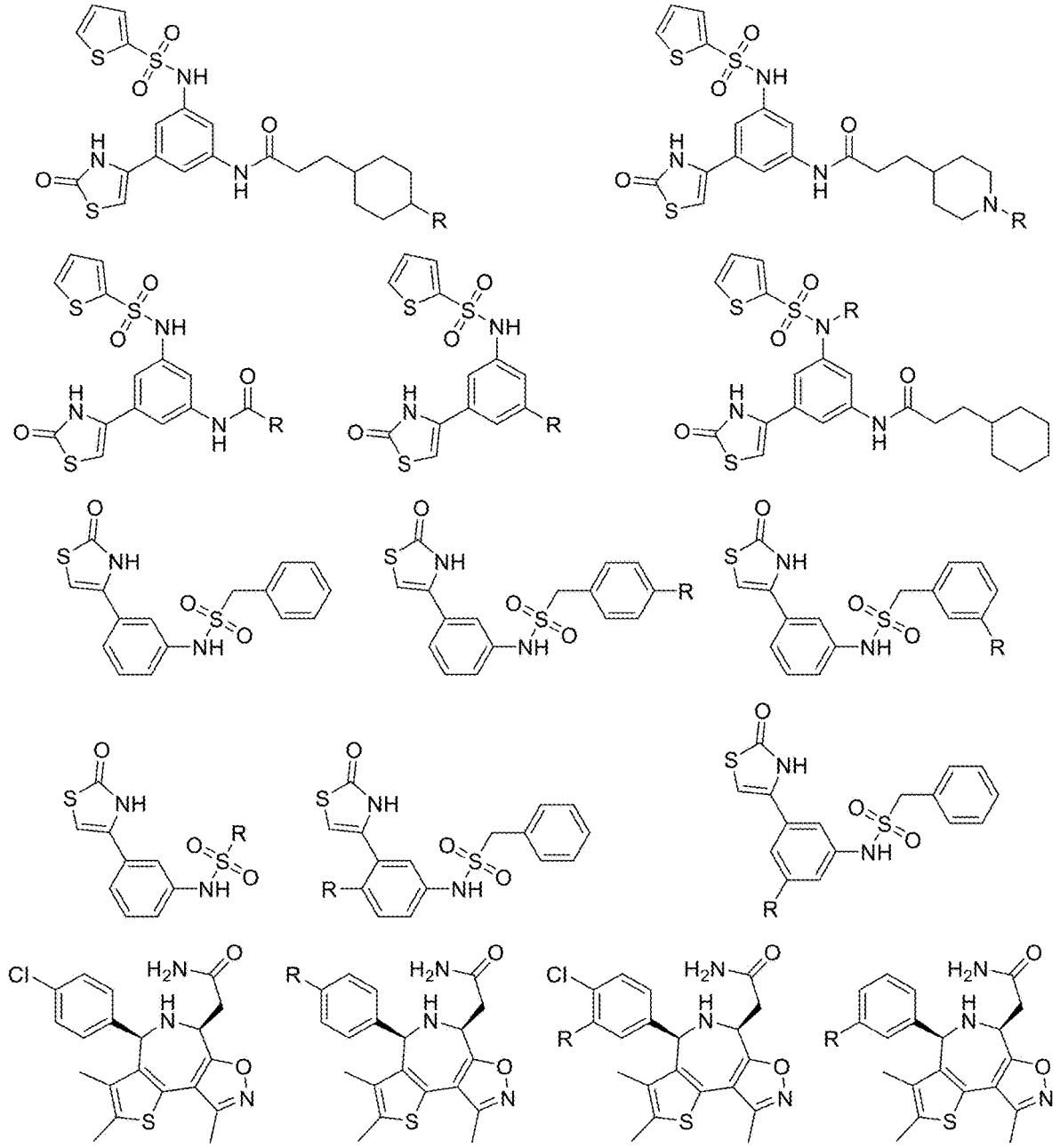


FIG. 8F

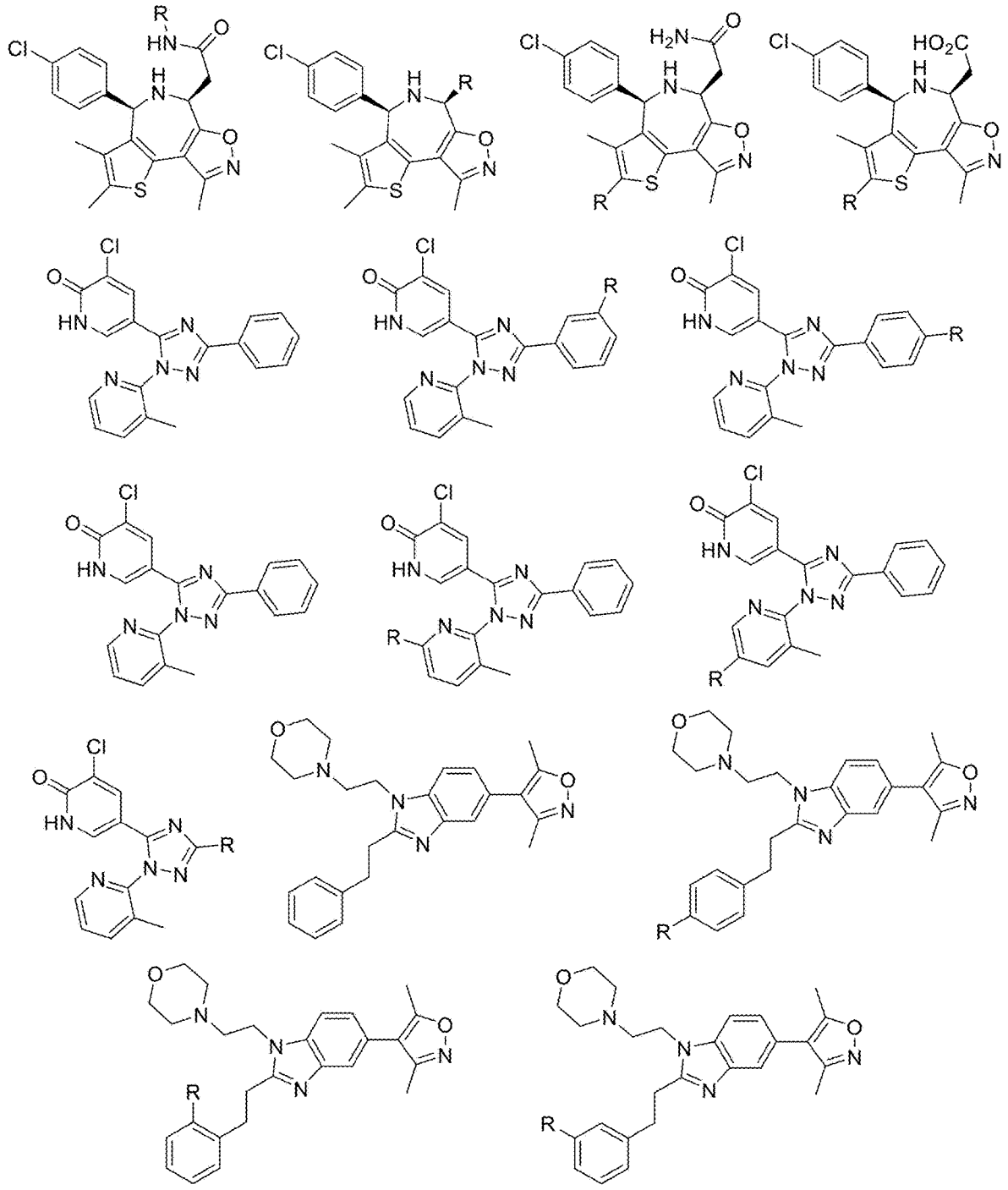


FIG. 8G

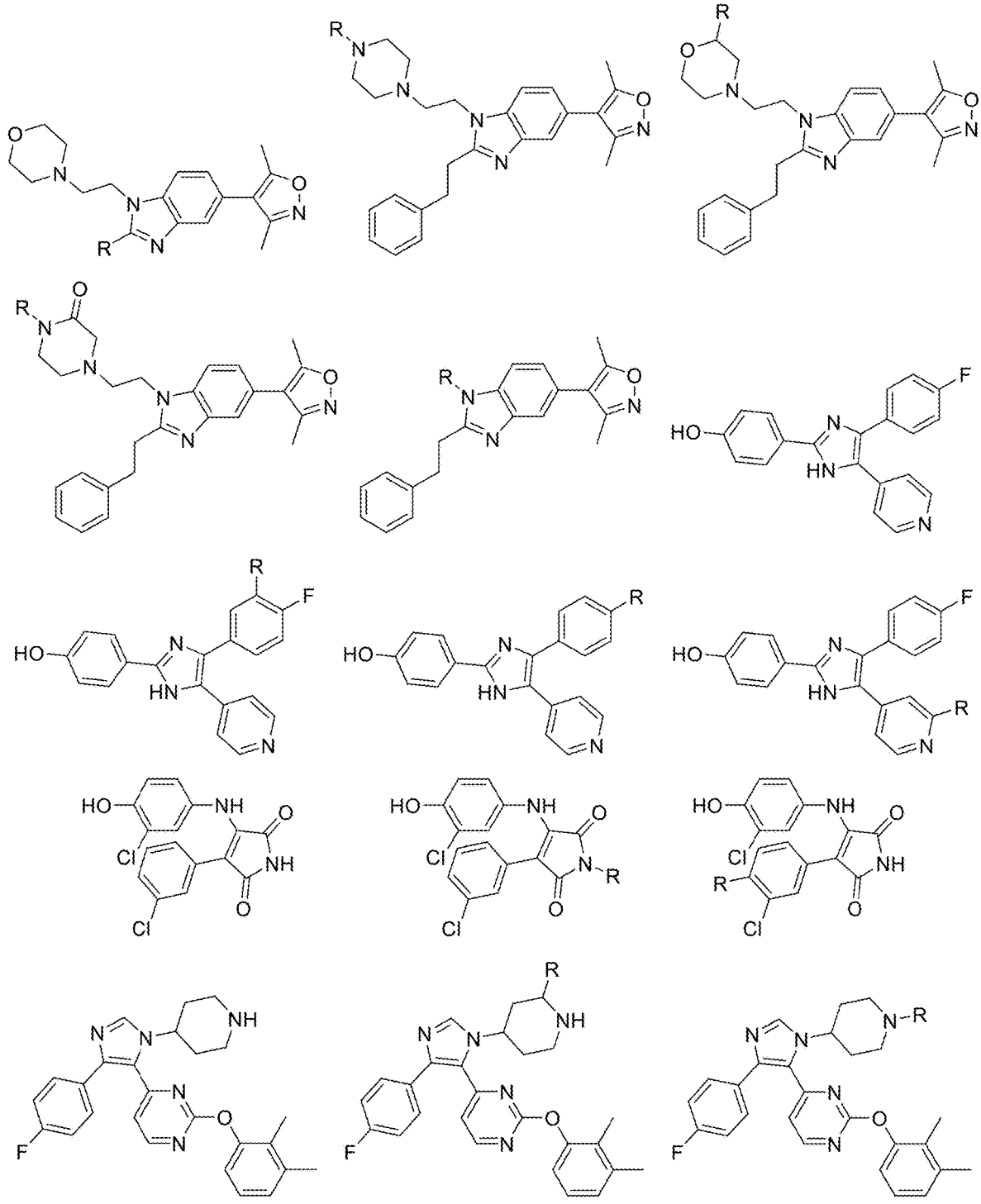


FIG. 8H

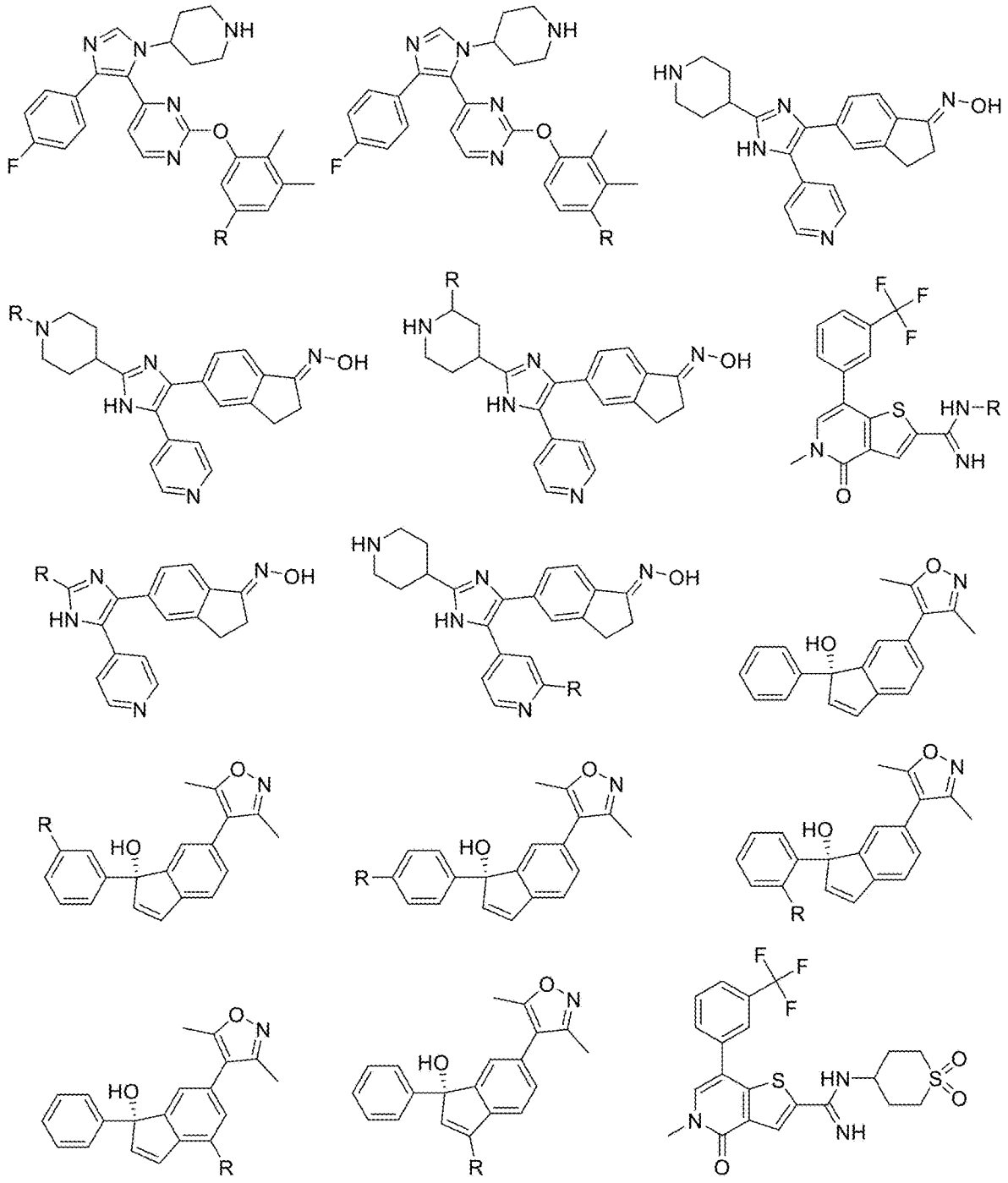


FIG. 8I

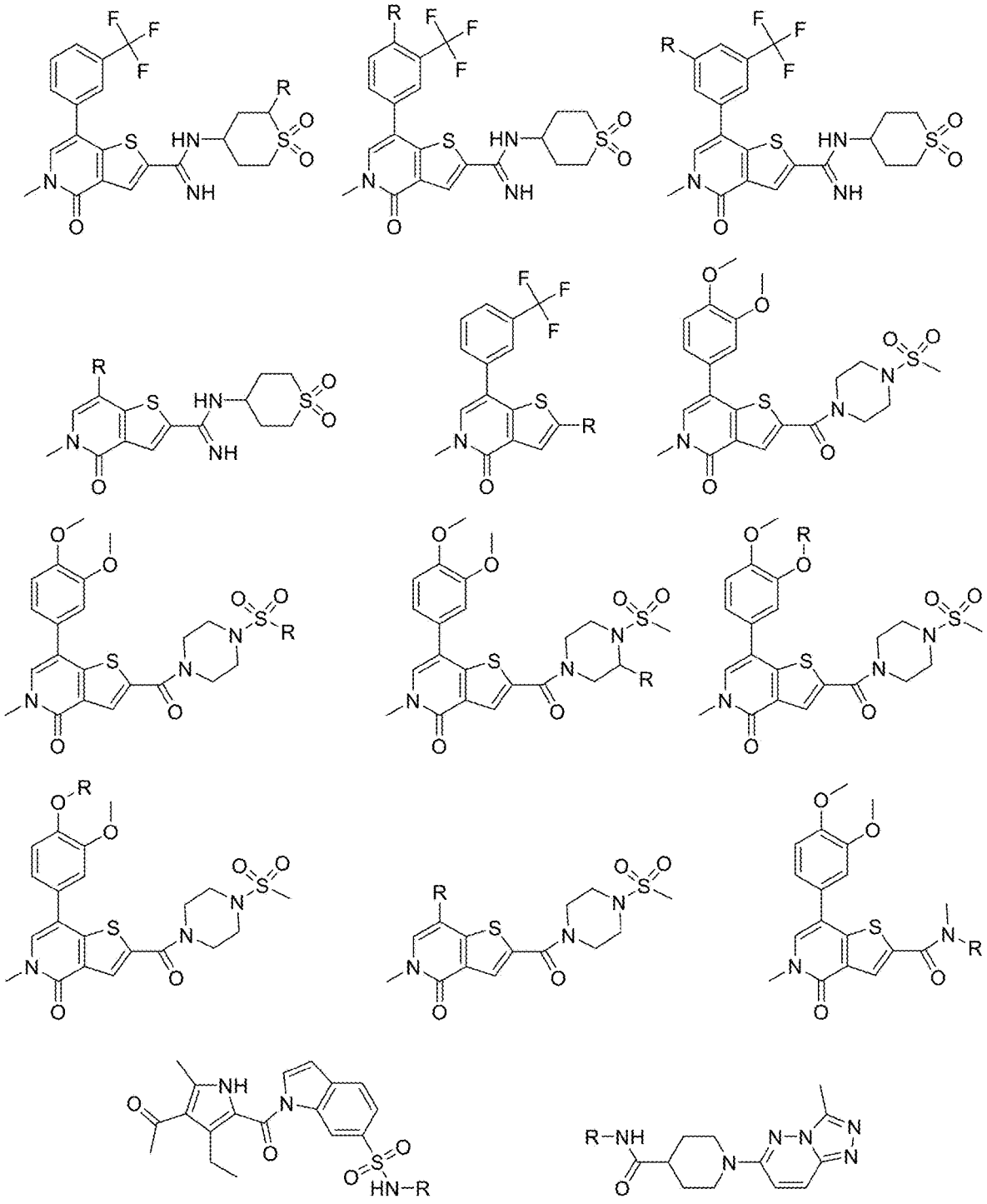


FIG. 8J

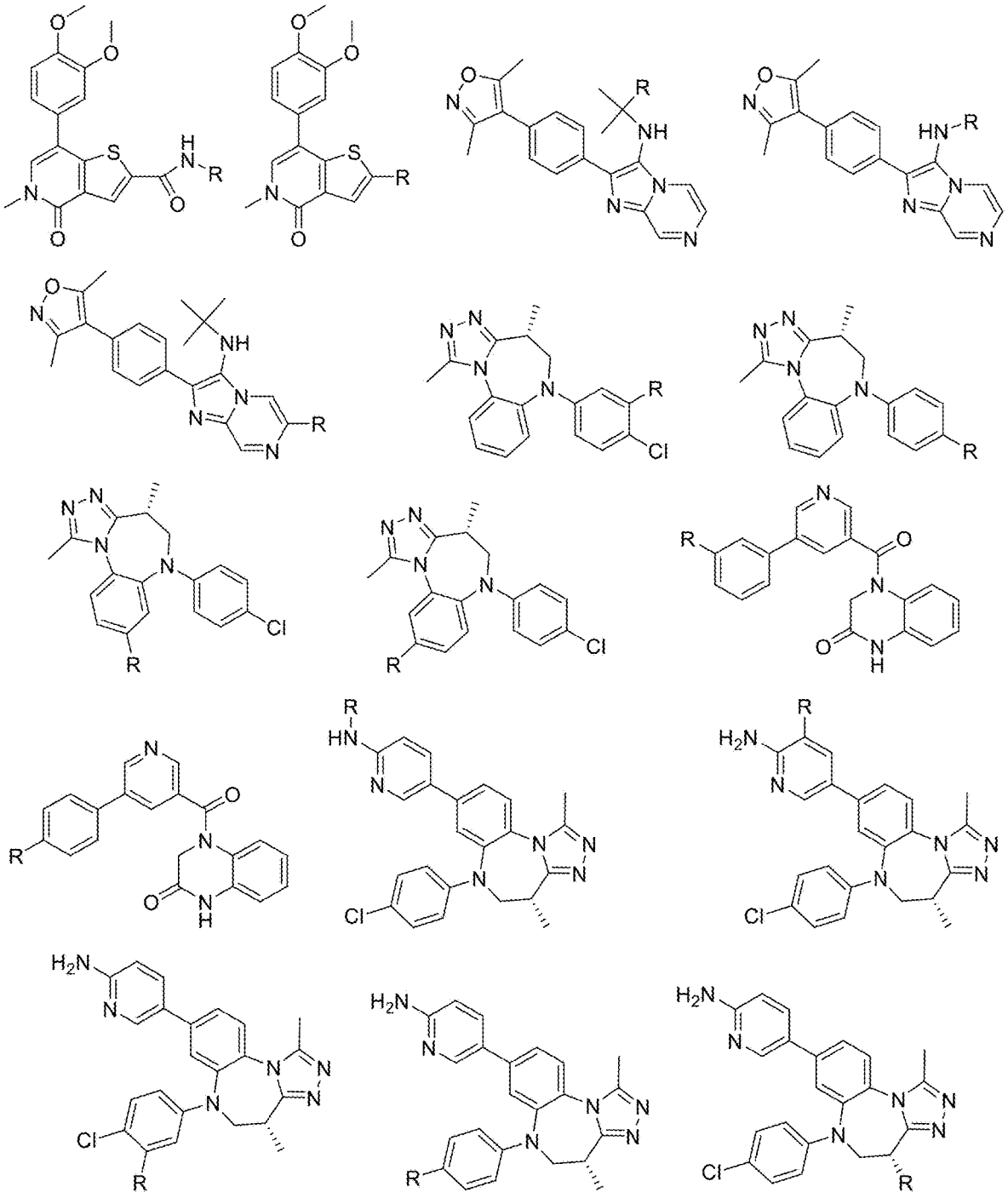


FIG. 8K

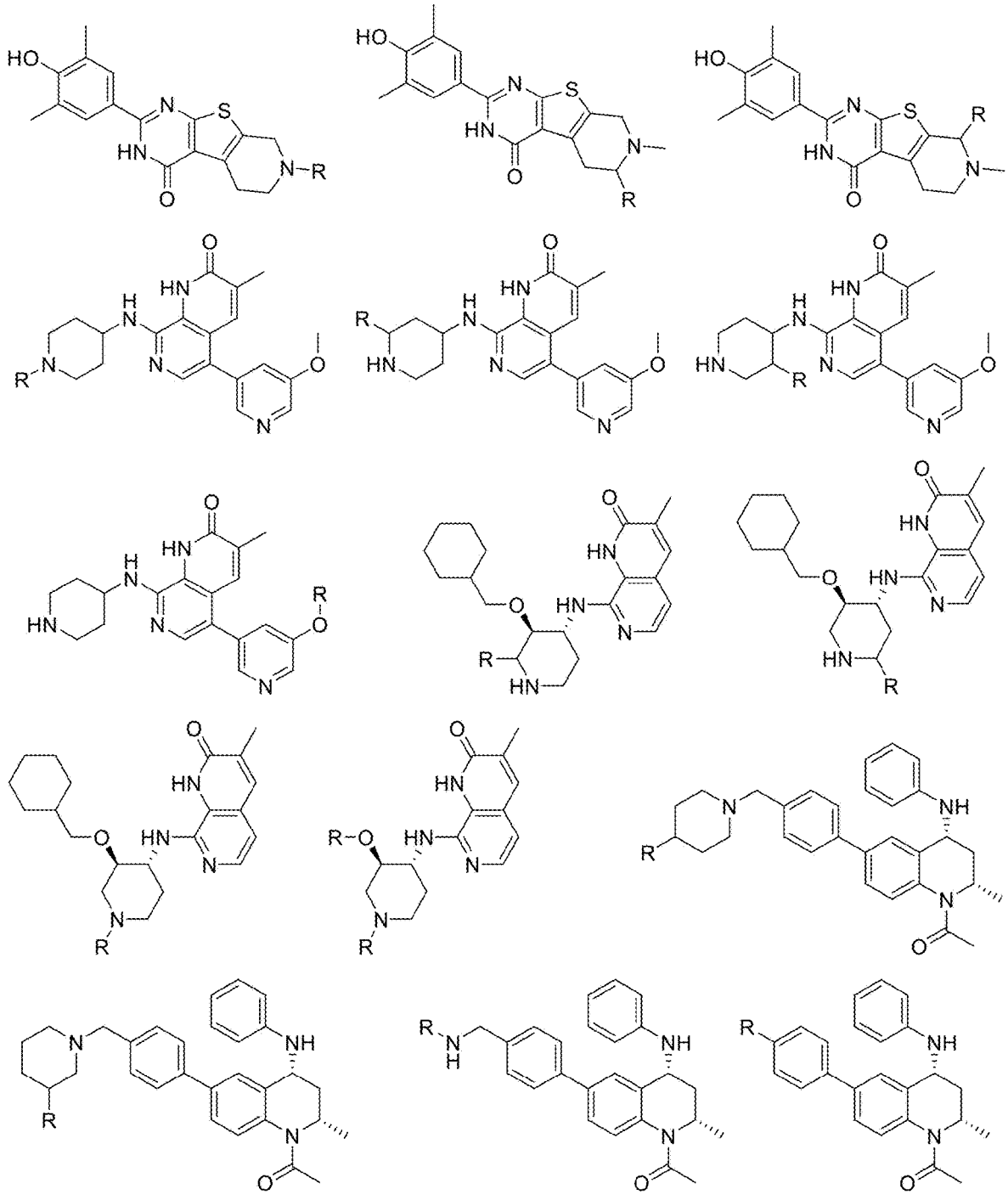


FIG. 8L

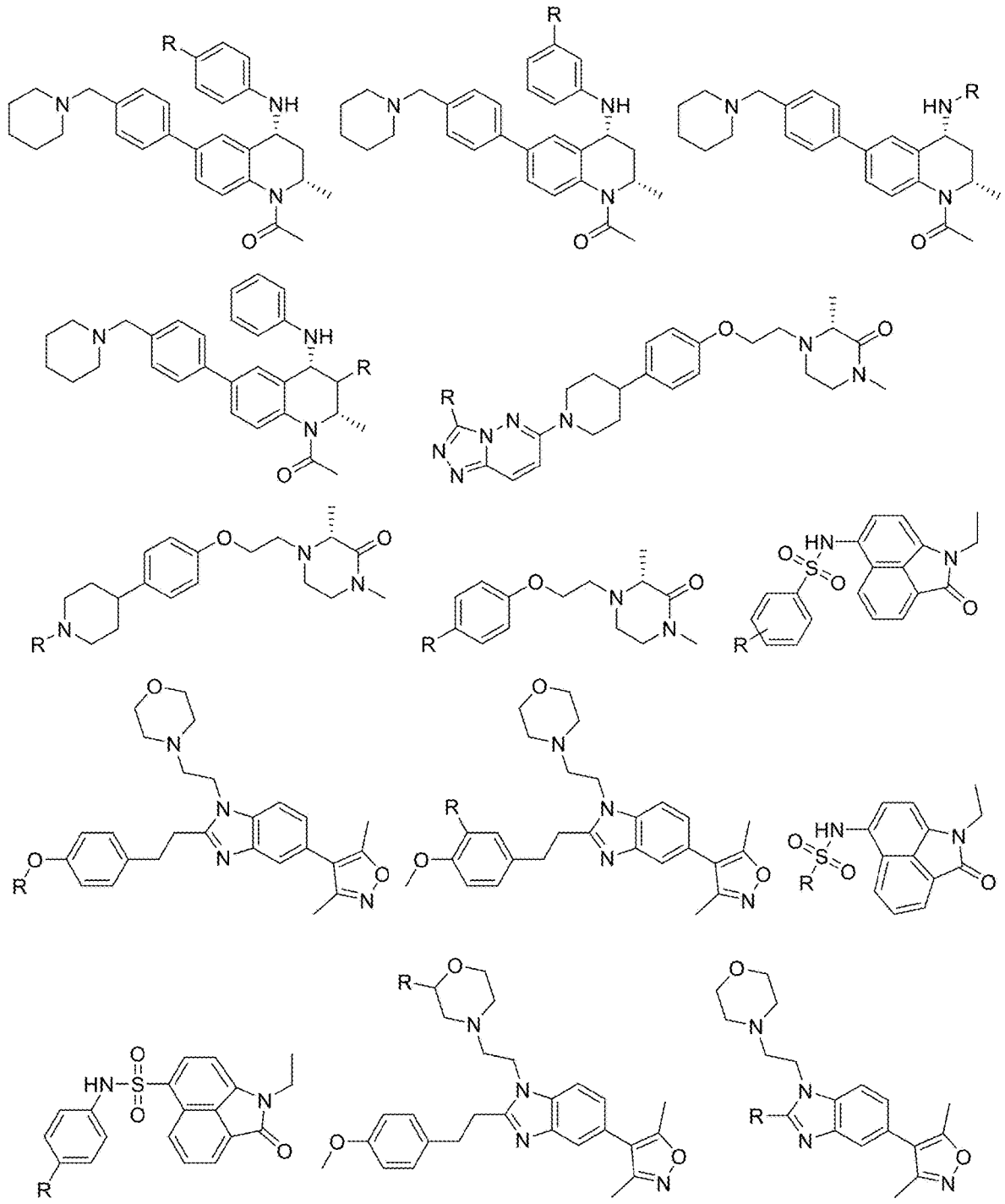


FIG. 8M

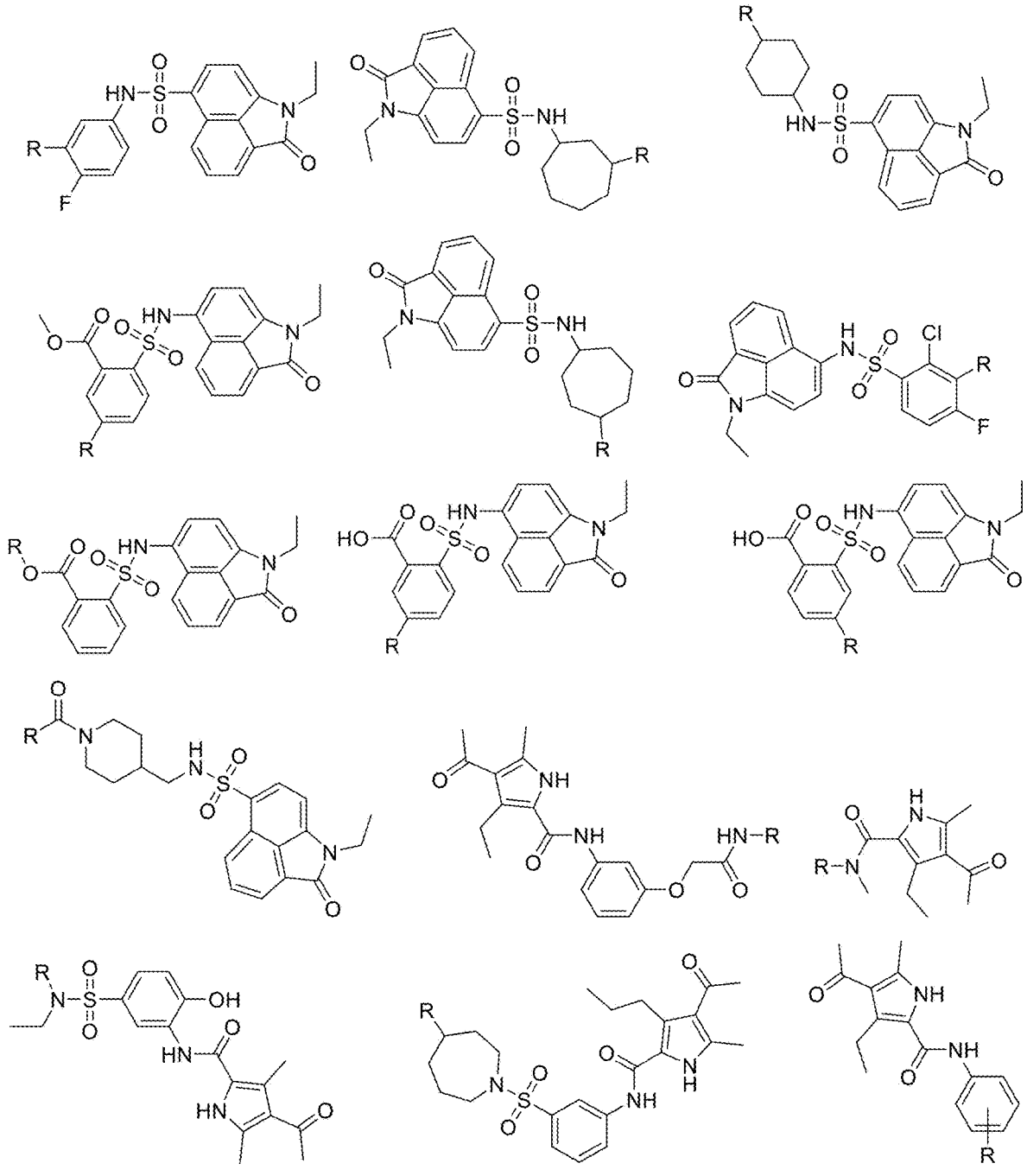


FIG. 8N

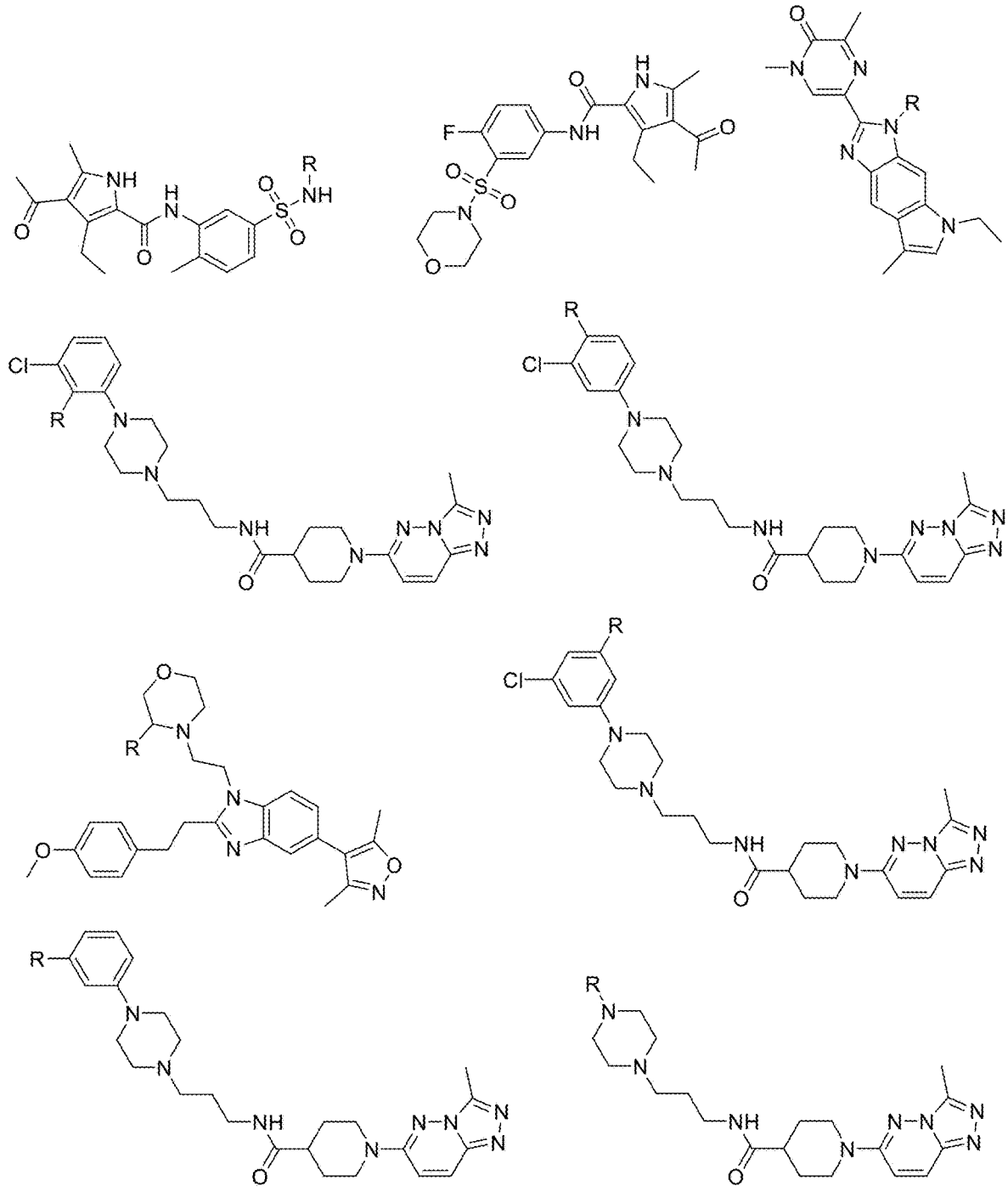


FIG. 8O

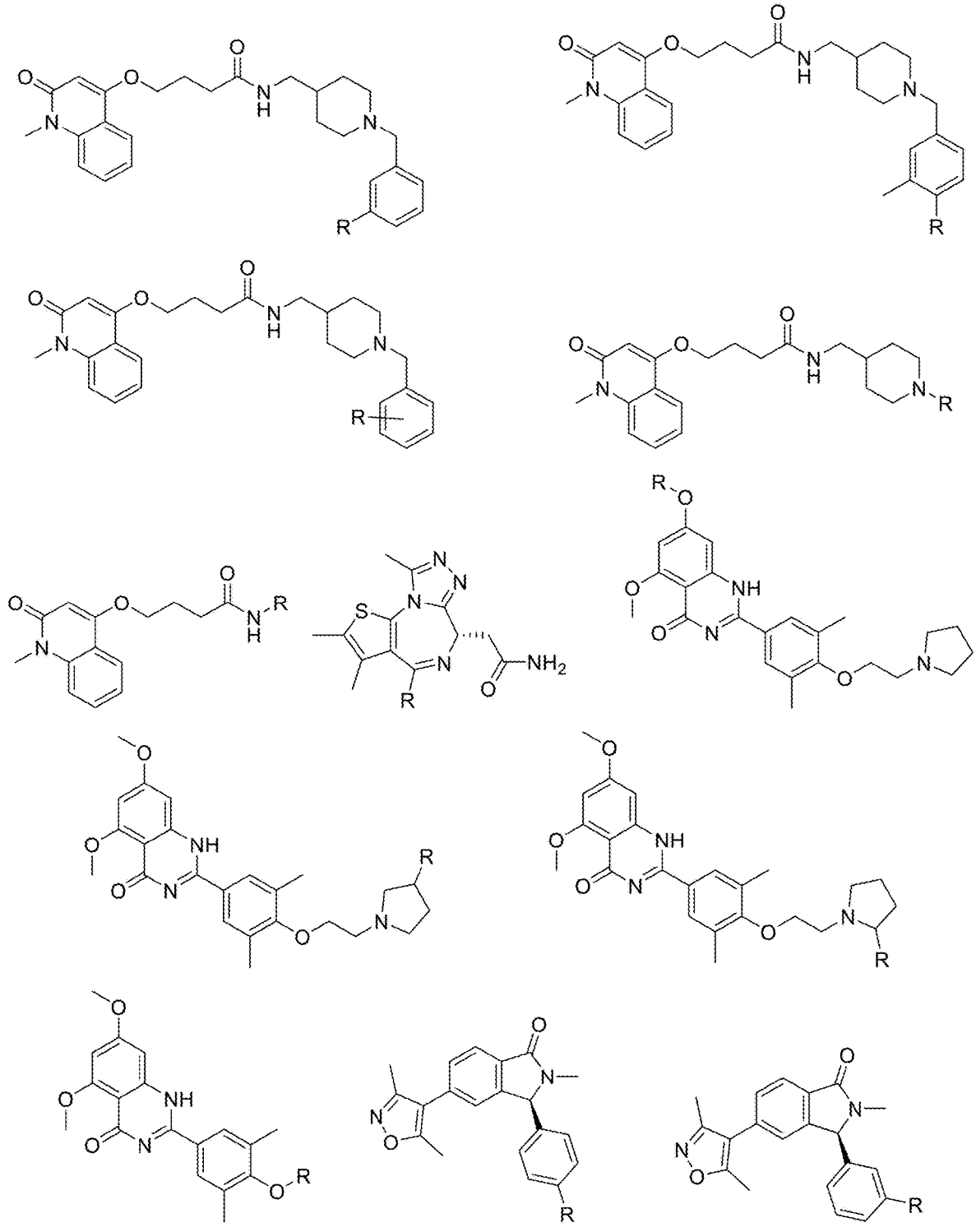


FIG. 8P

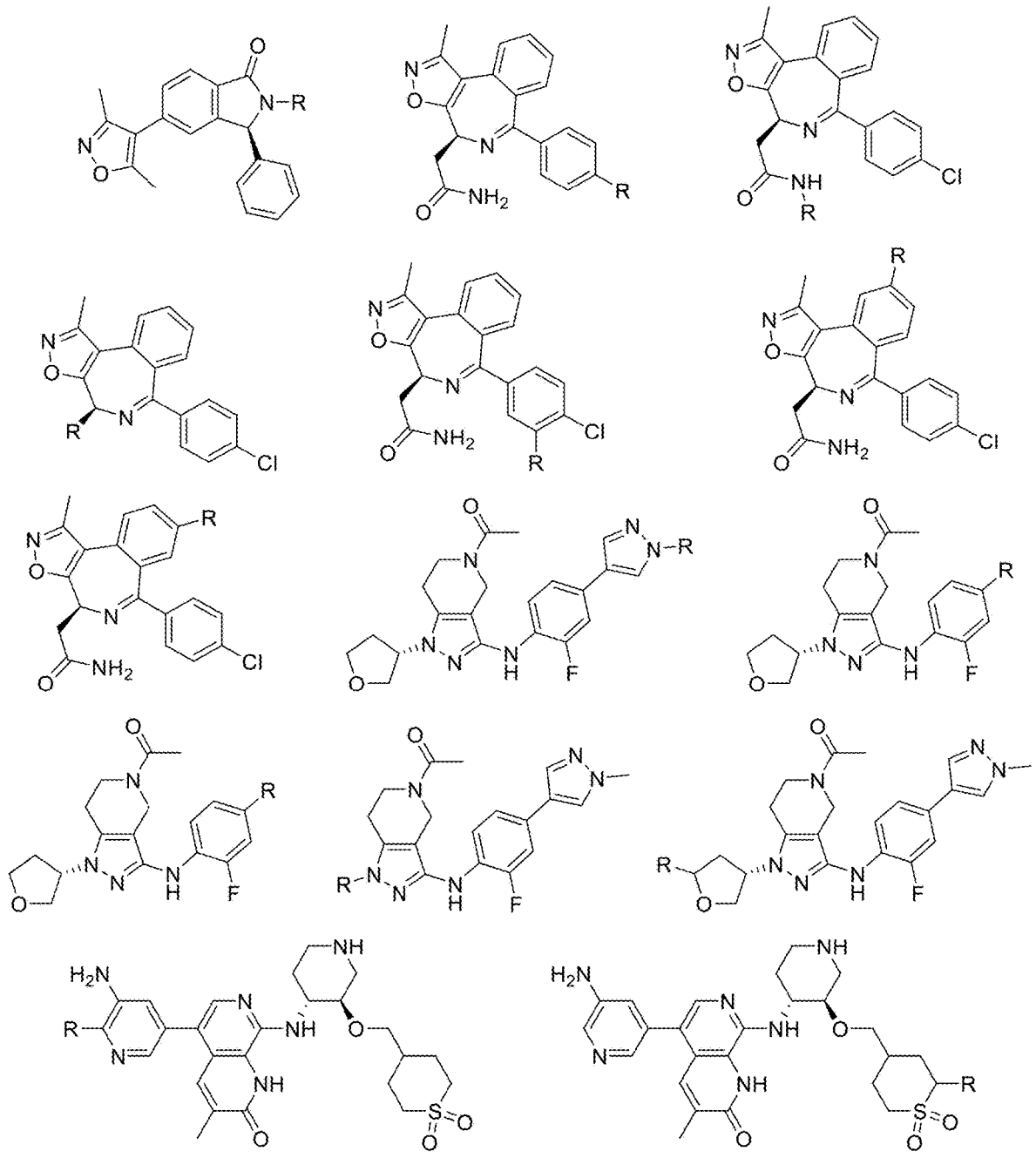


FIG. 8Q

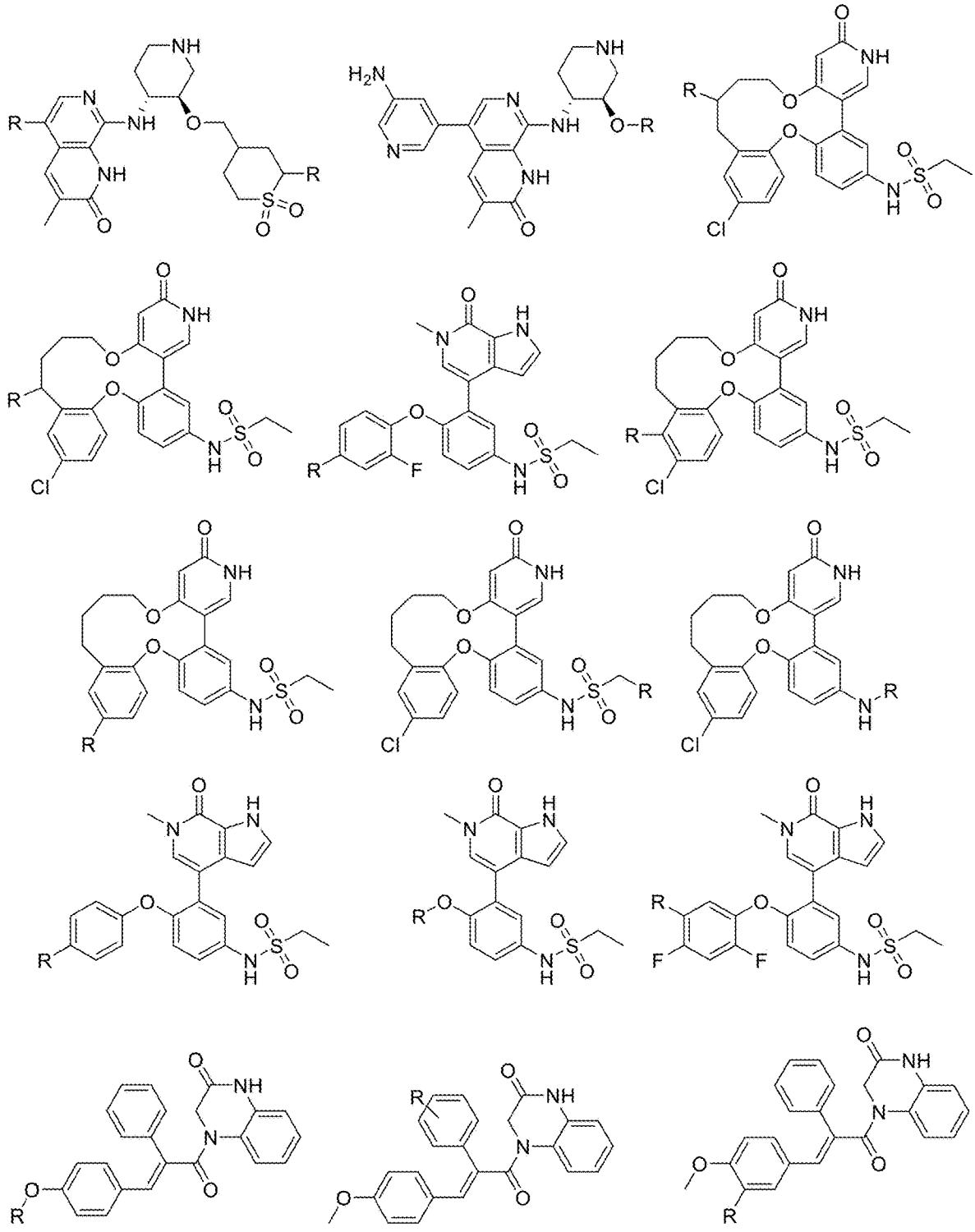


FIG. 8R

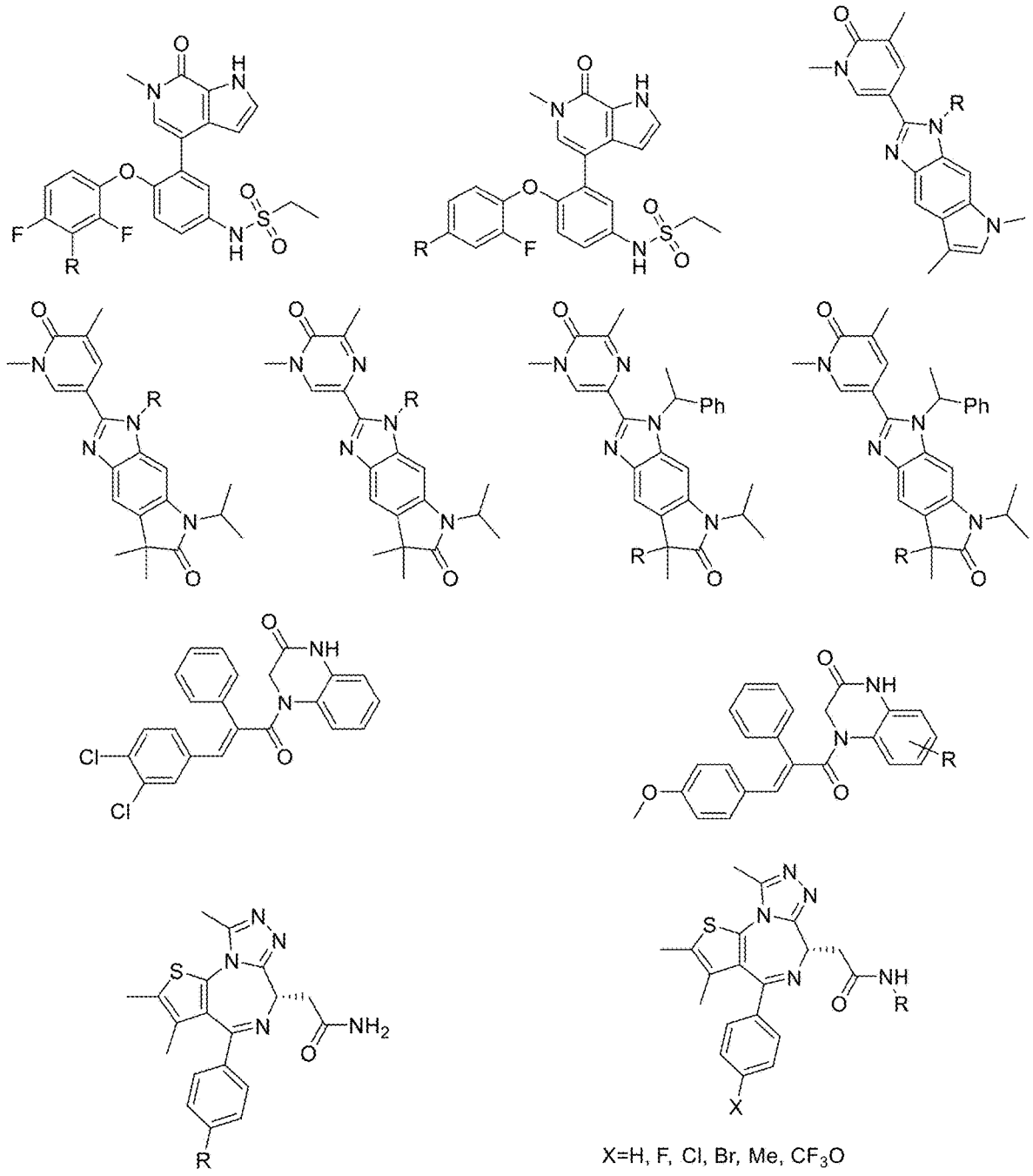
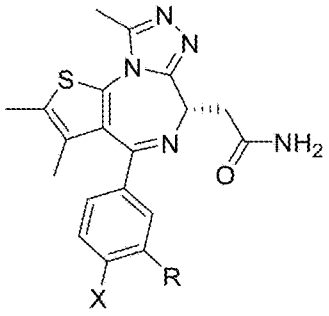


FIG. 8S



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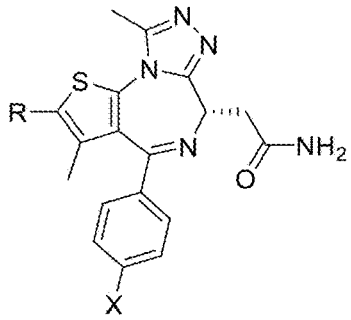
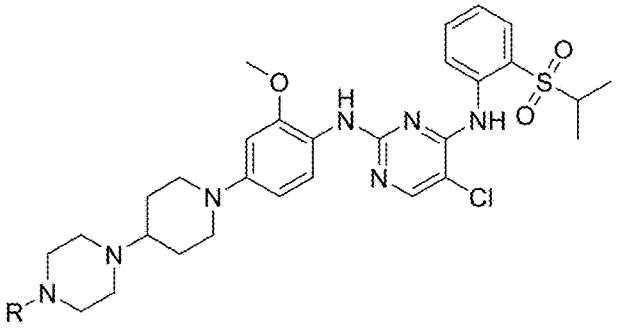
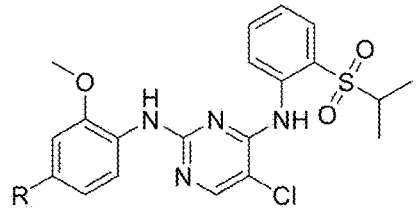
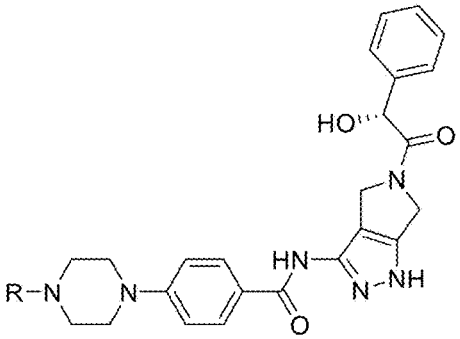


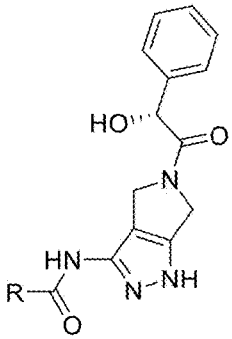
X=H, F, Cl, Br, Me, CF_3O

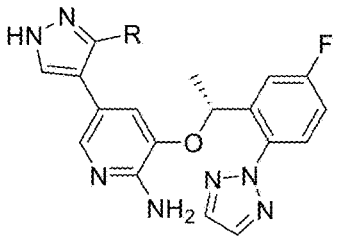
FIG. 8T

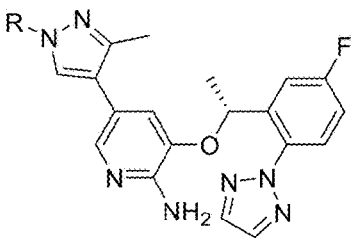


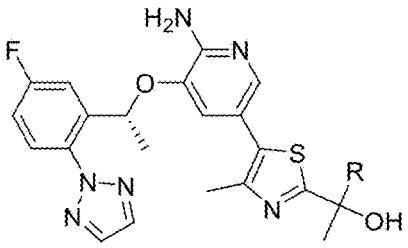












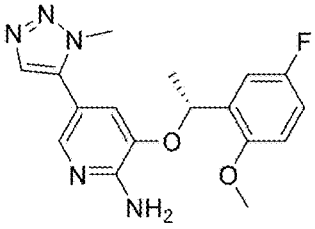


FIG. 8U

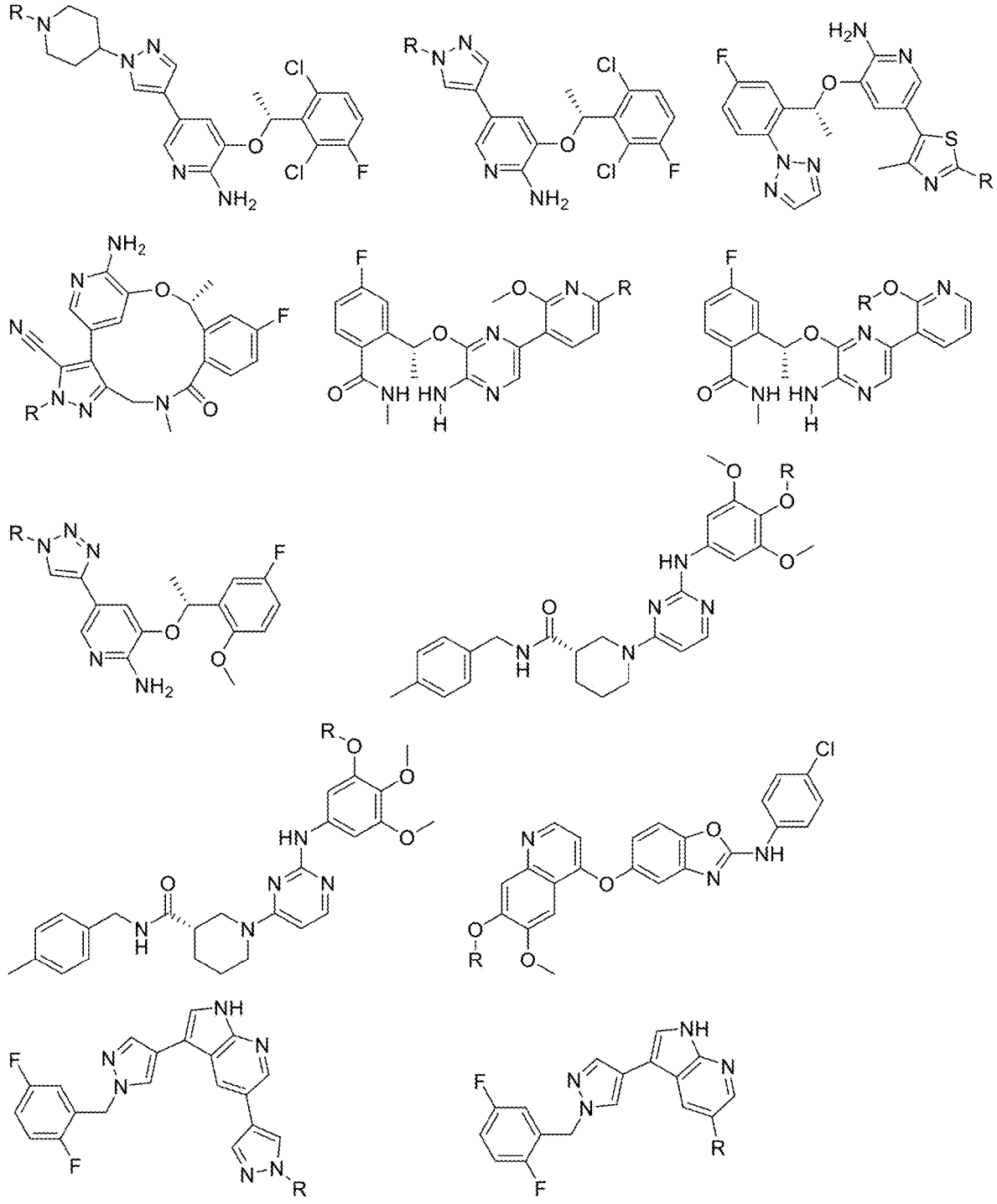


FIG. 8V

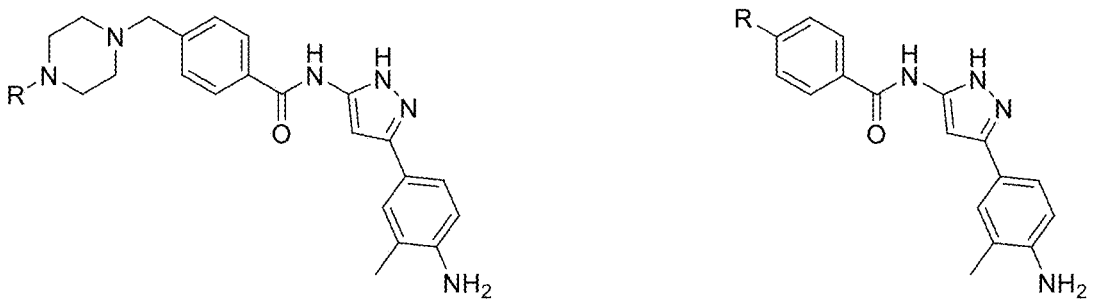


FIG. 8W

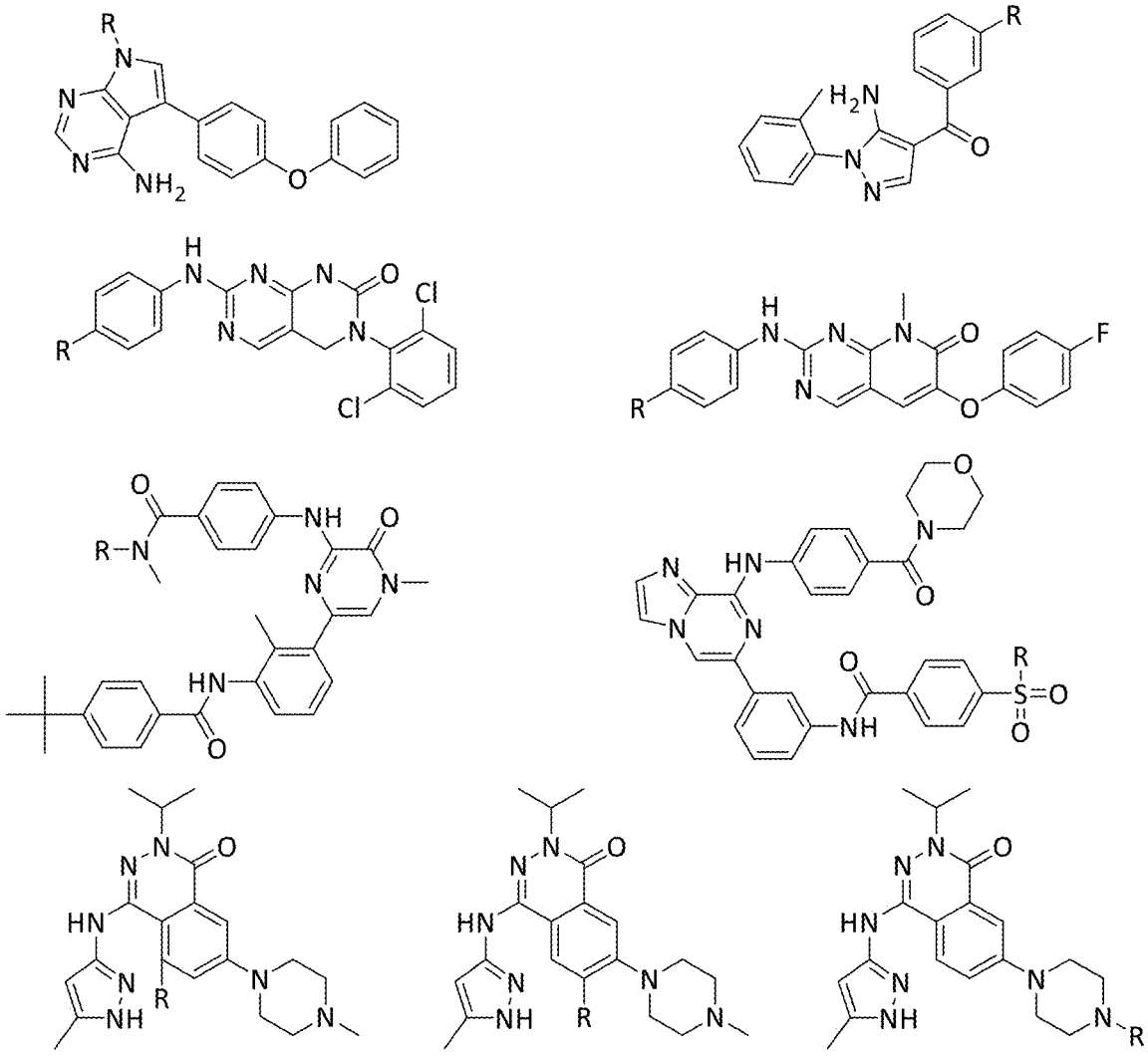


FIG. 8X

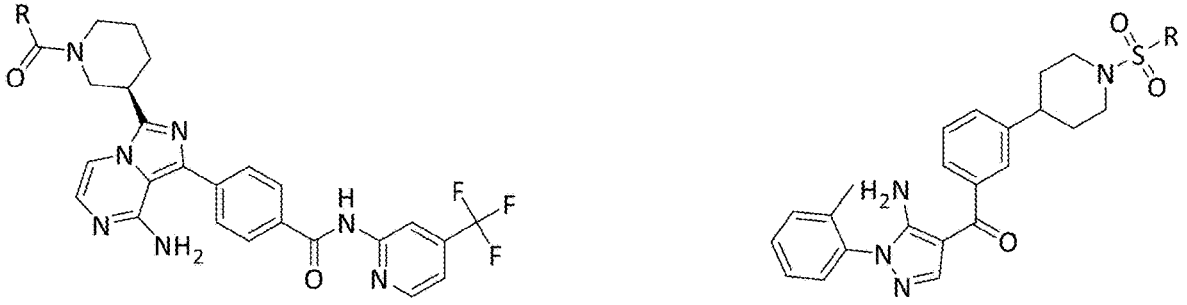


FIG. 8Y

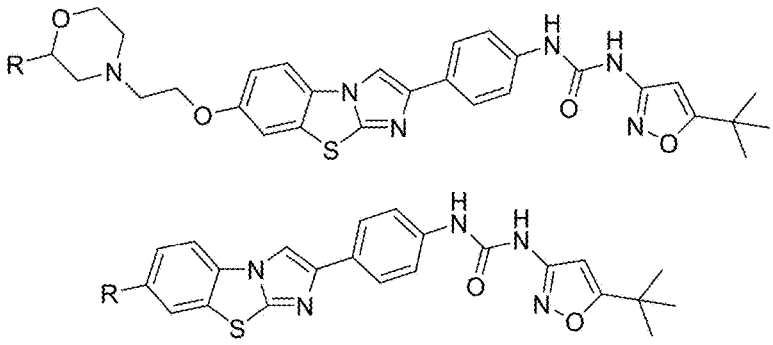


FIG. 8Z

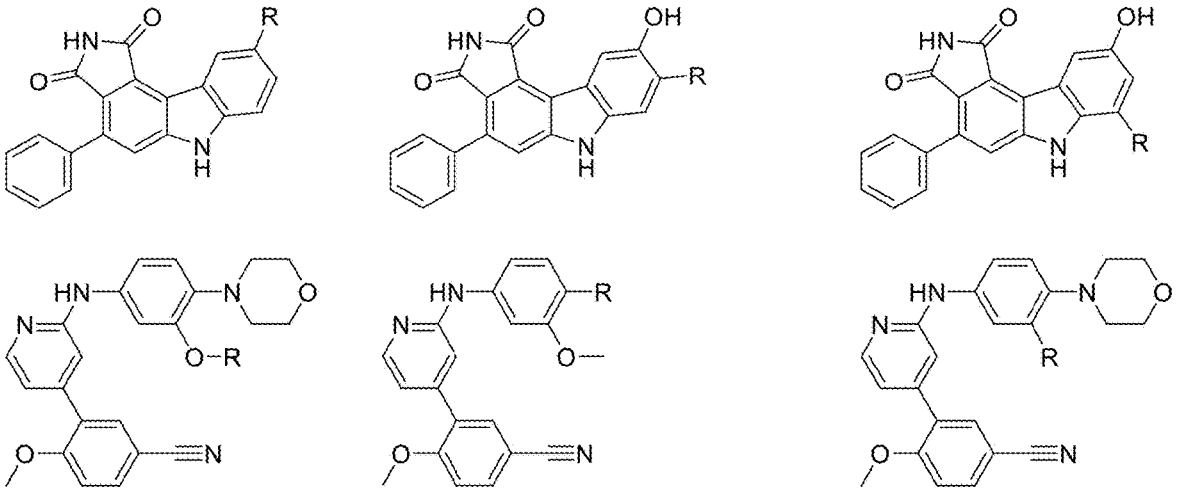


FIG. 8AA

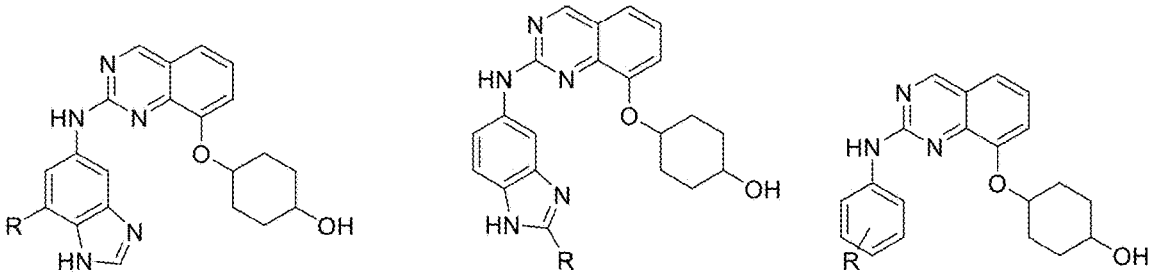


FIG. 8BB

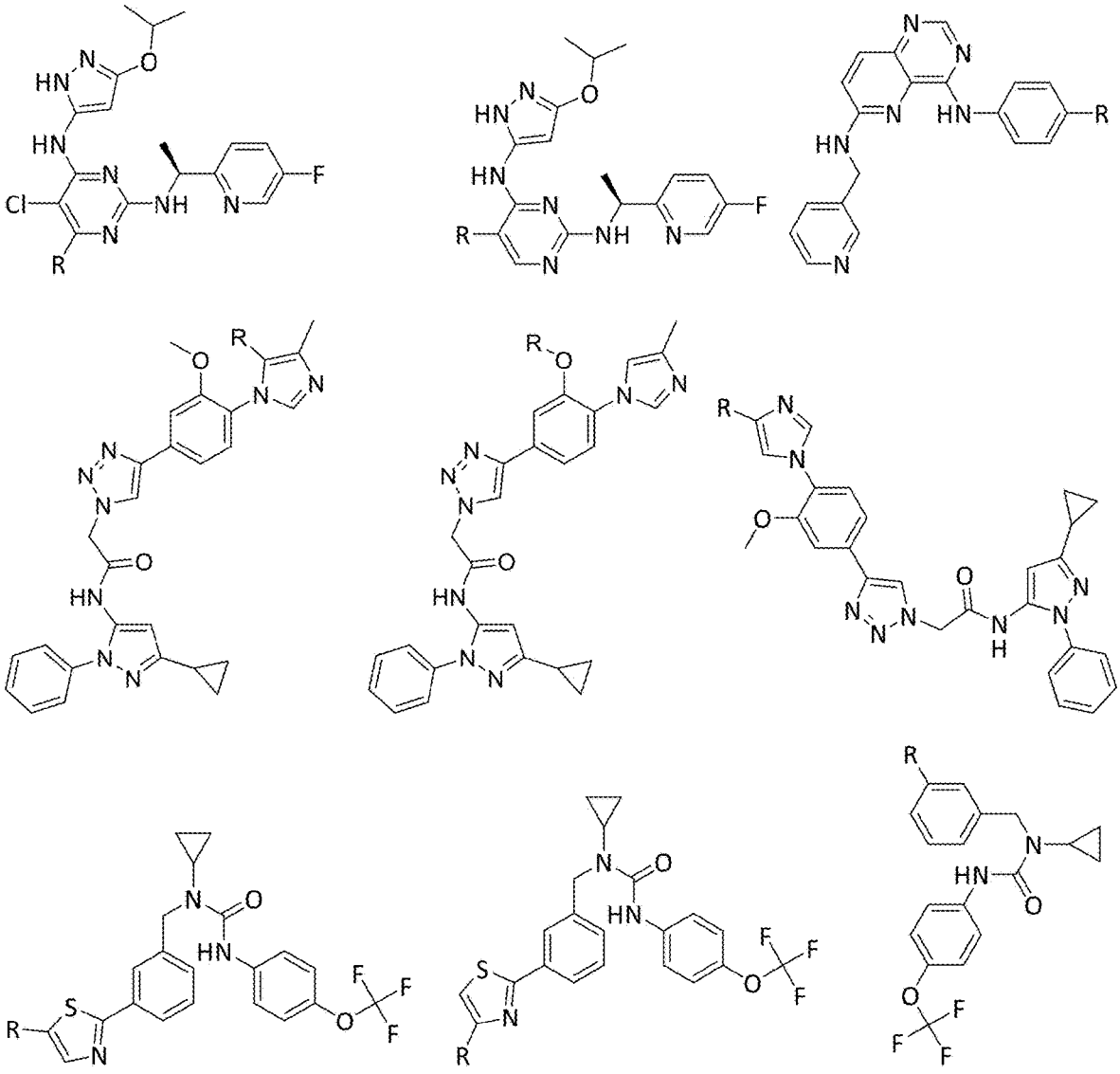


FIG. 8CC

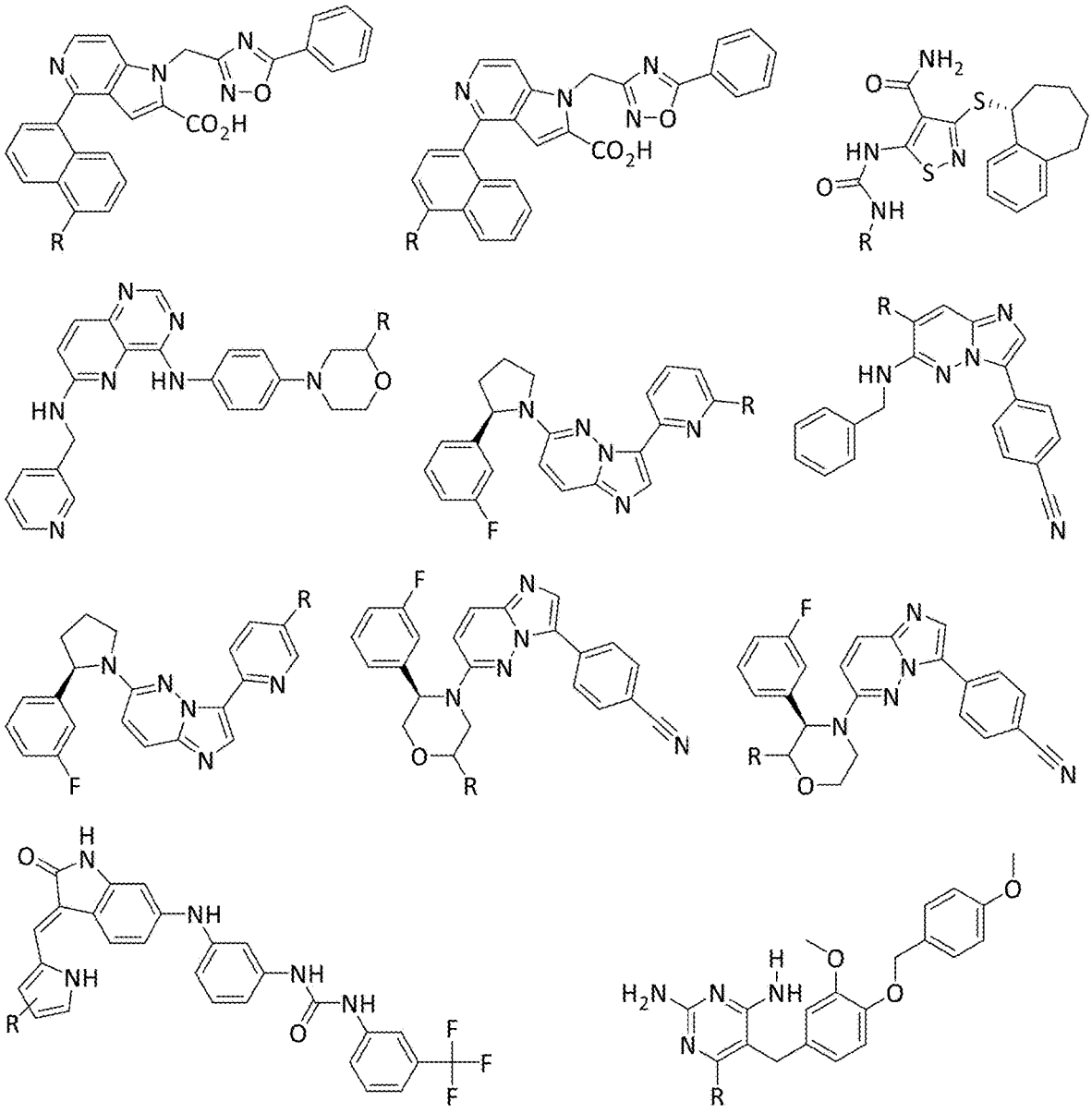


FIG. 8DD

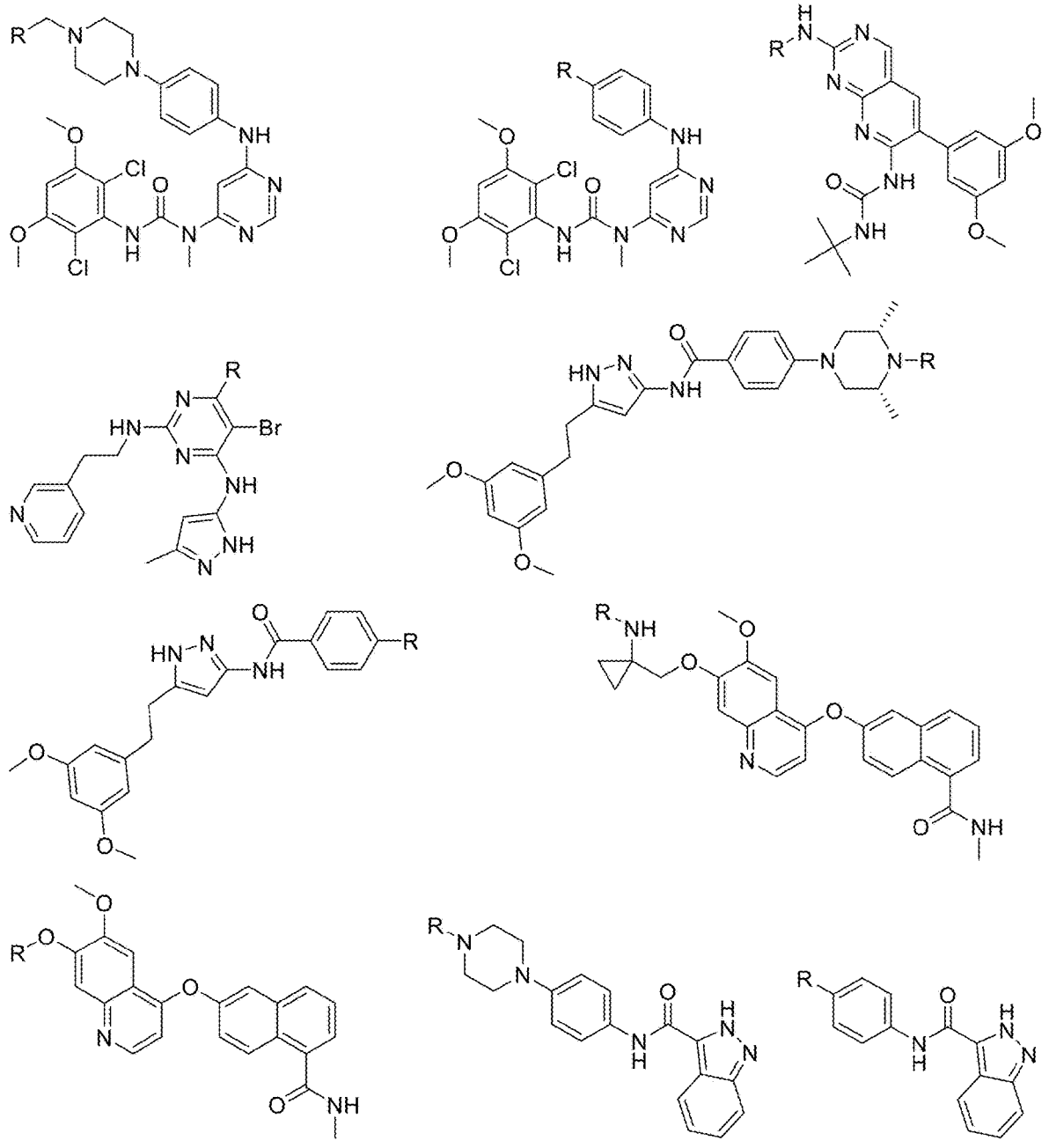


FIG. 8EE

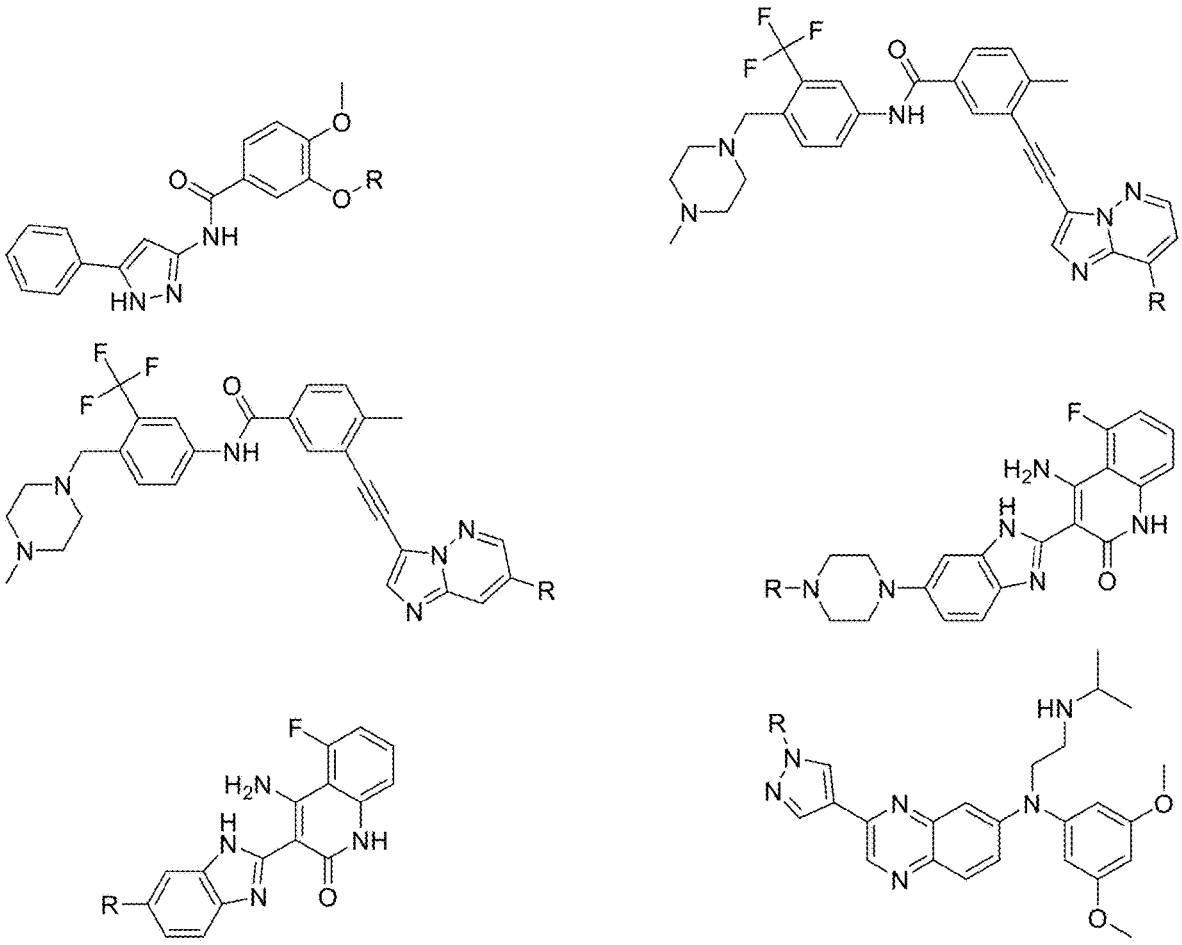


FIG. 8FF

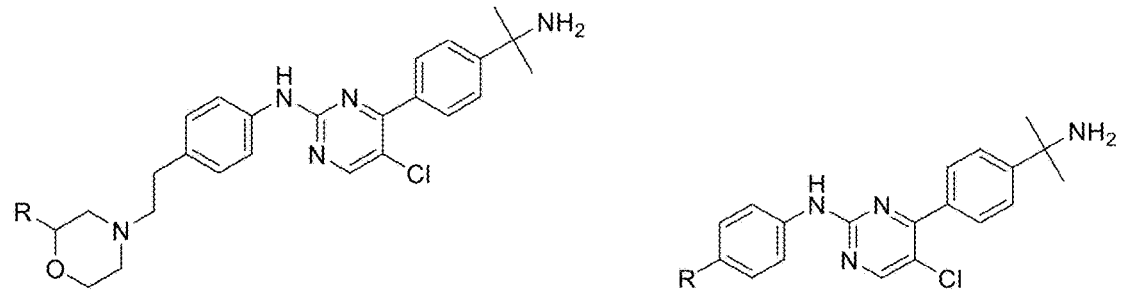


FIG. 8GG

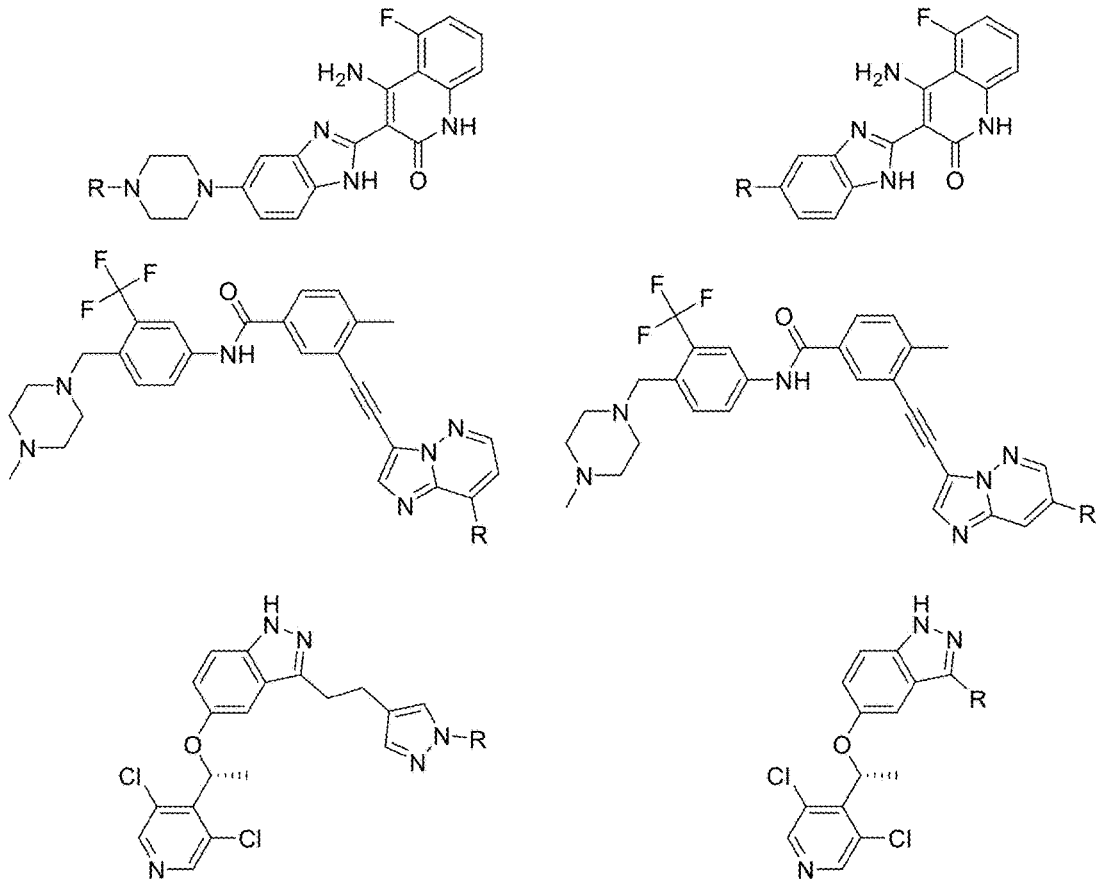


FIG. 8HH

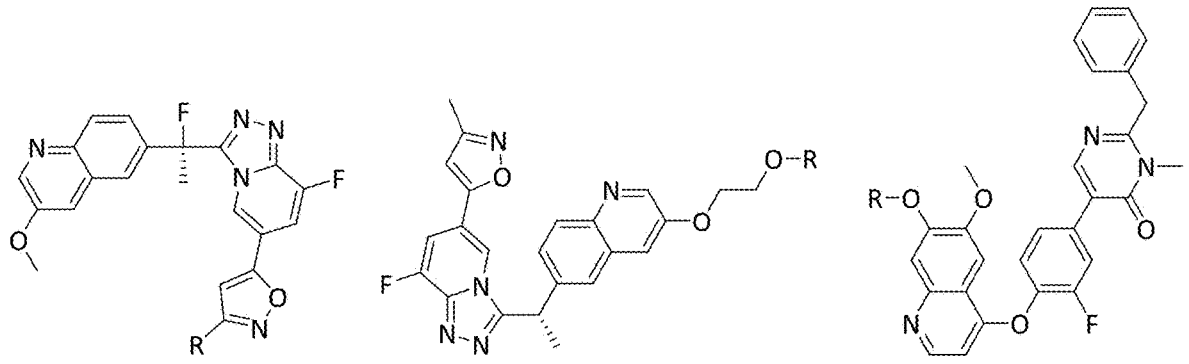


FIG. 8II

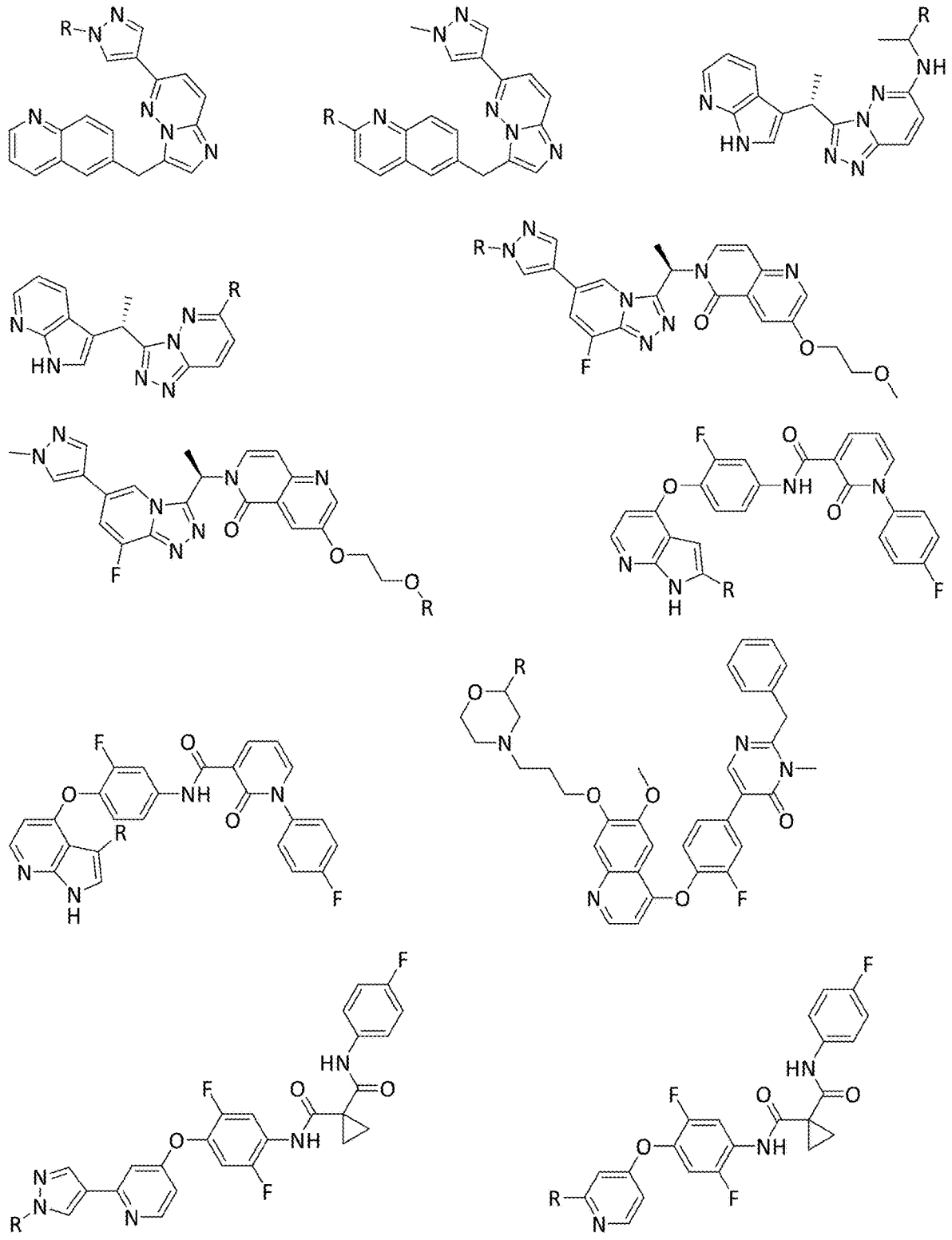


FIG. 8JJ

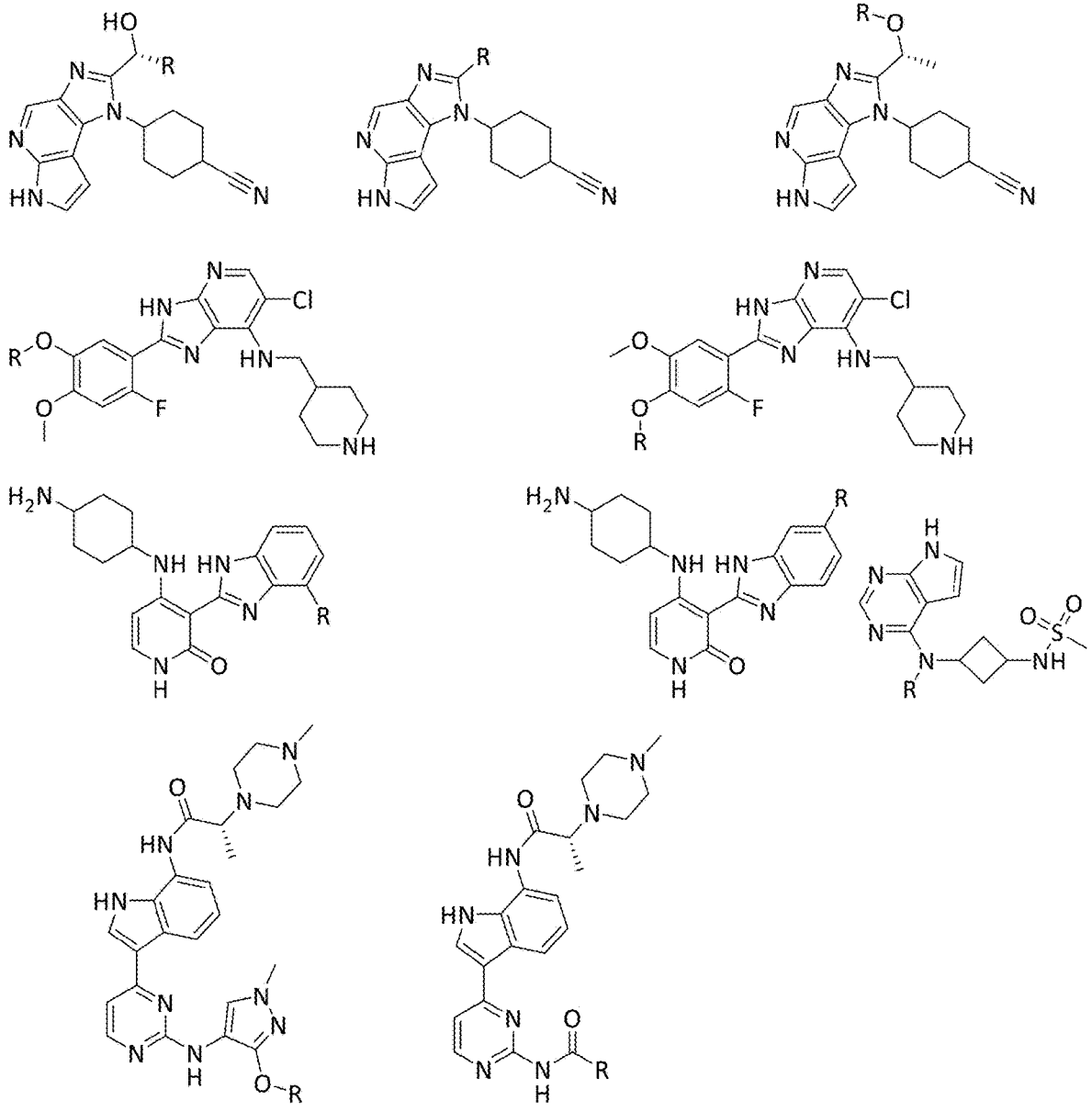


FIG. 8KK

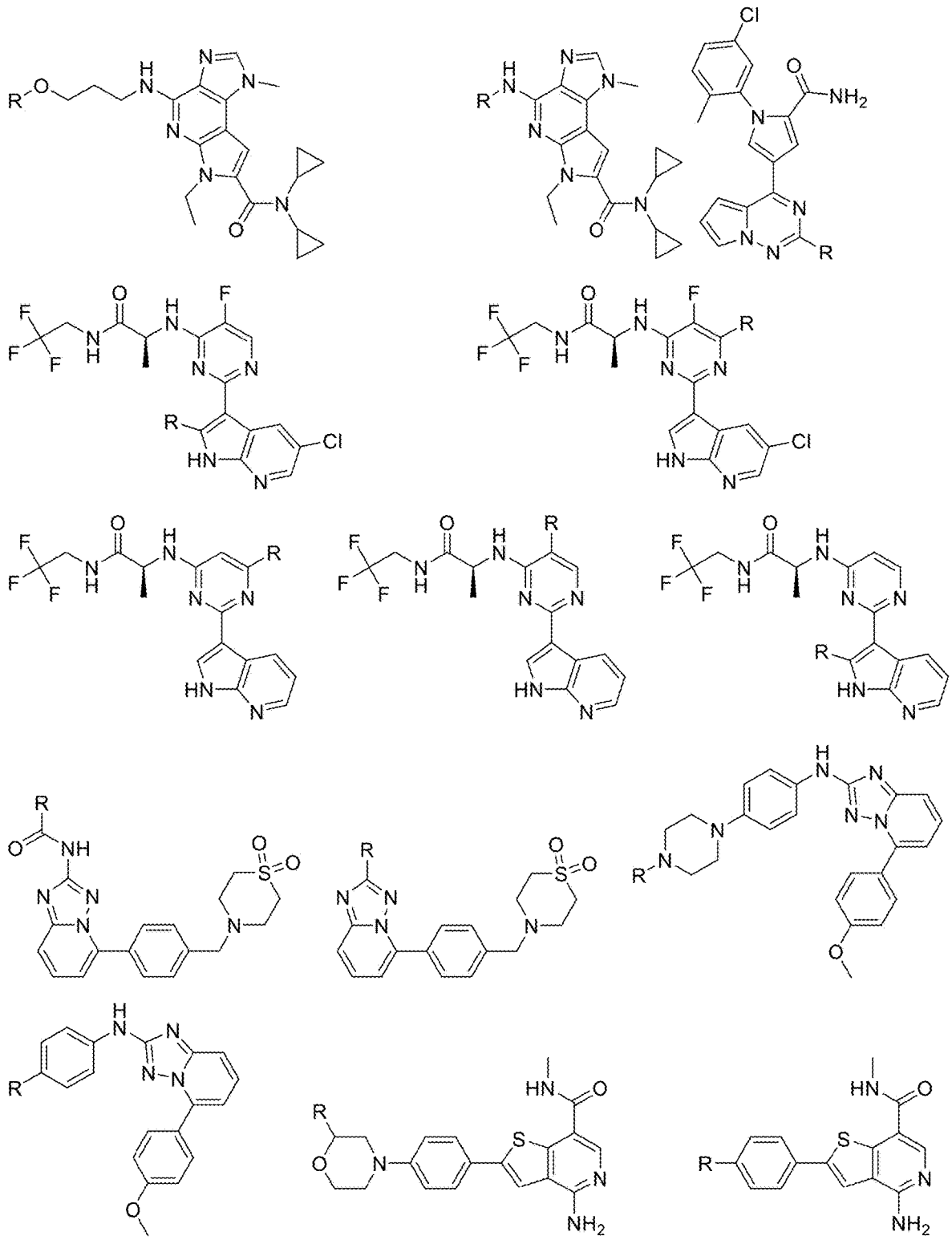


FIG. 8LL

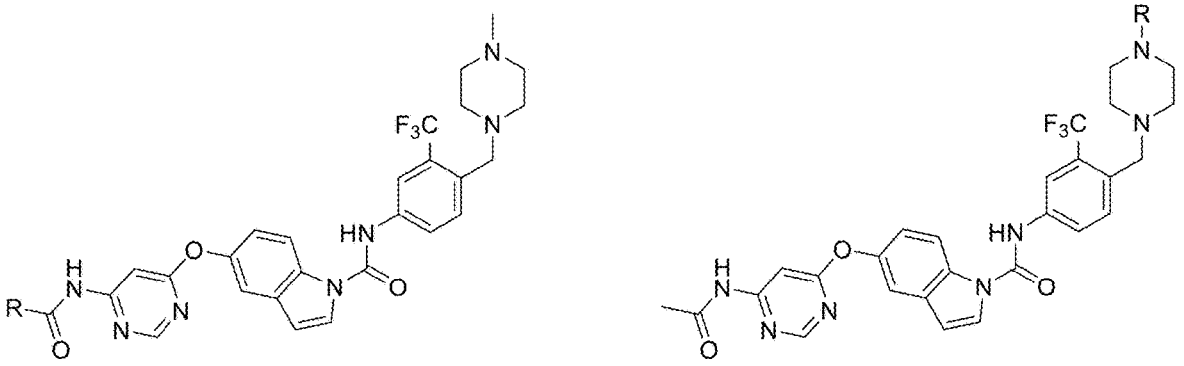


FIG. 8MM

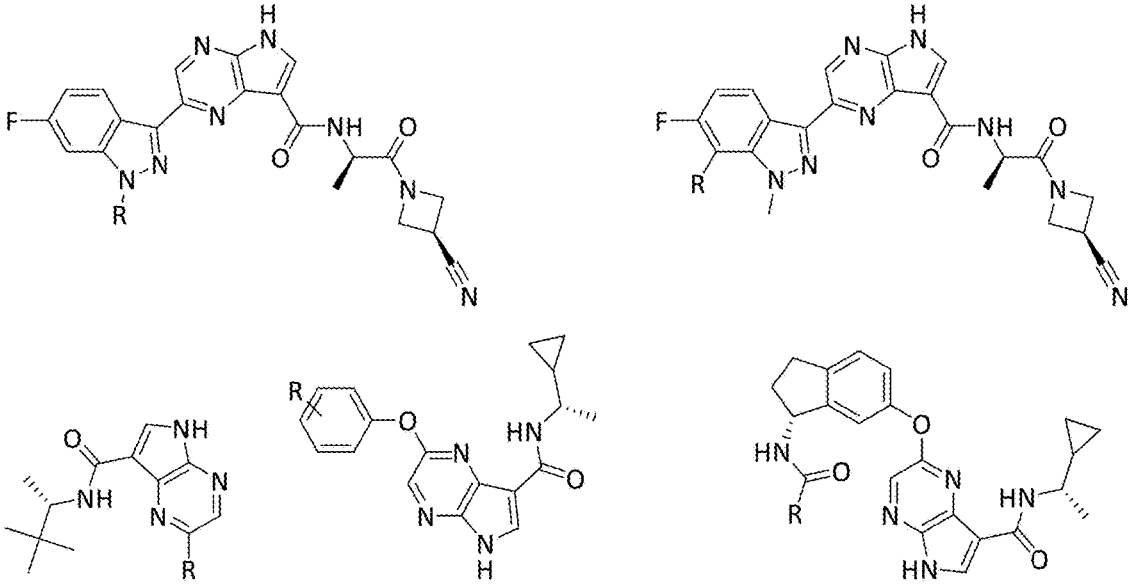


FIG. 8NN

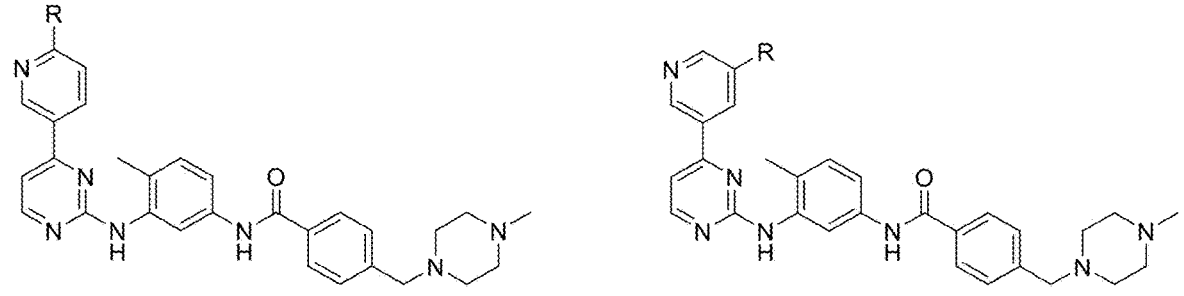


FIG. 8OO

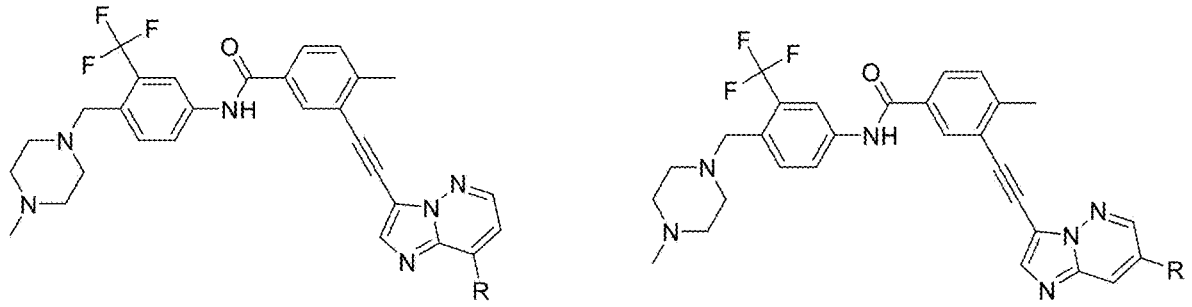


FIG. 8PP

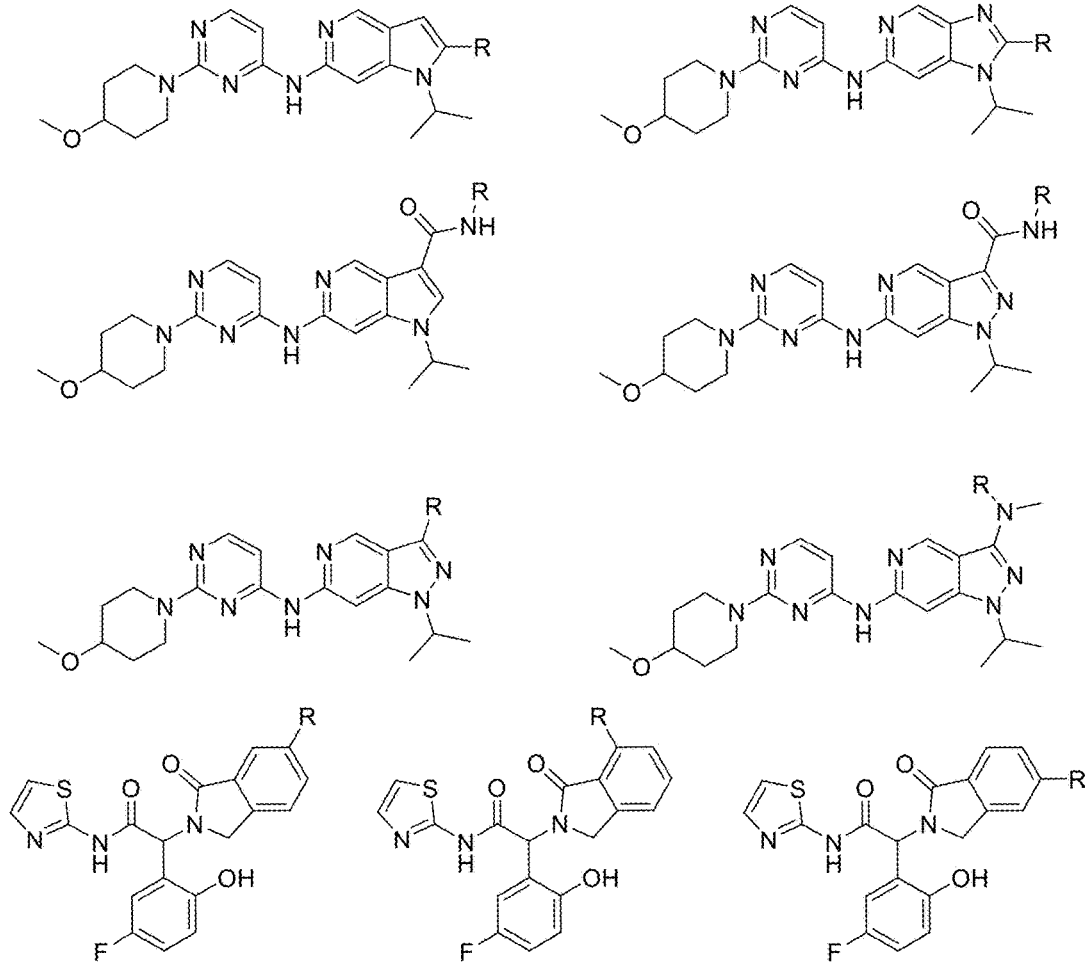


FIG. 8QQ

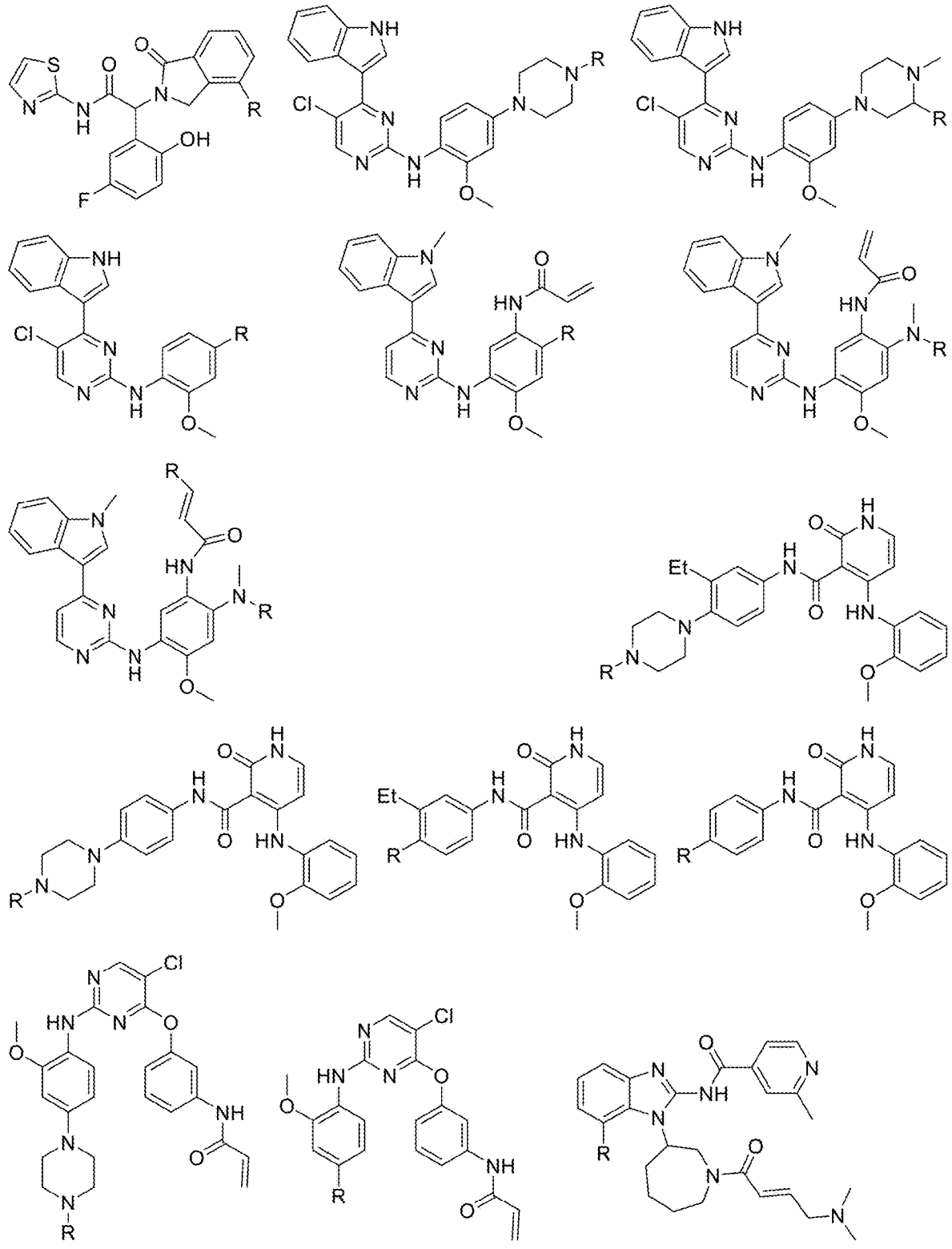


FIG. 8RR

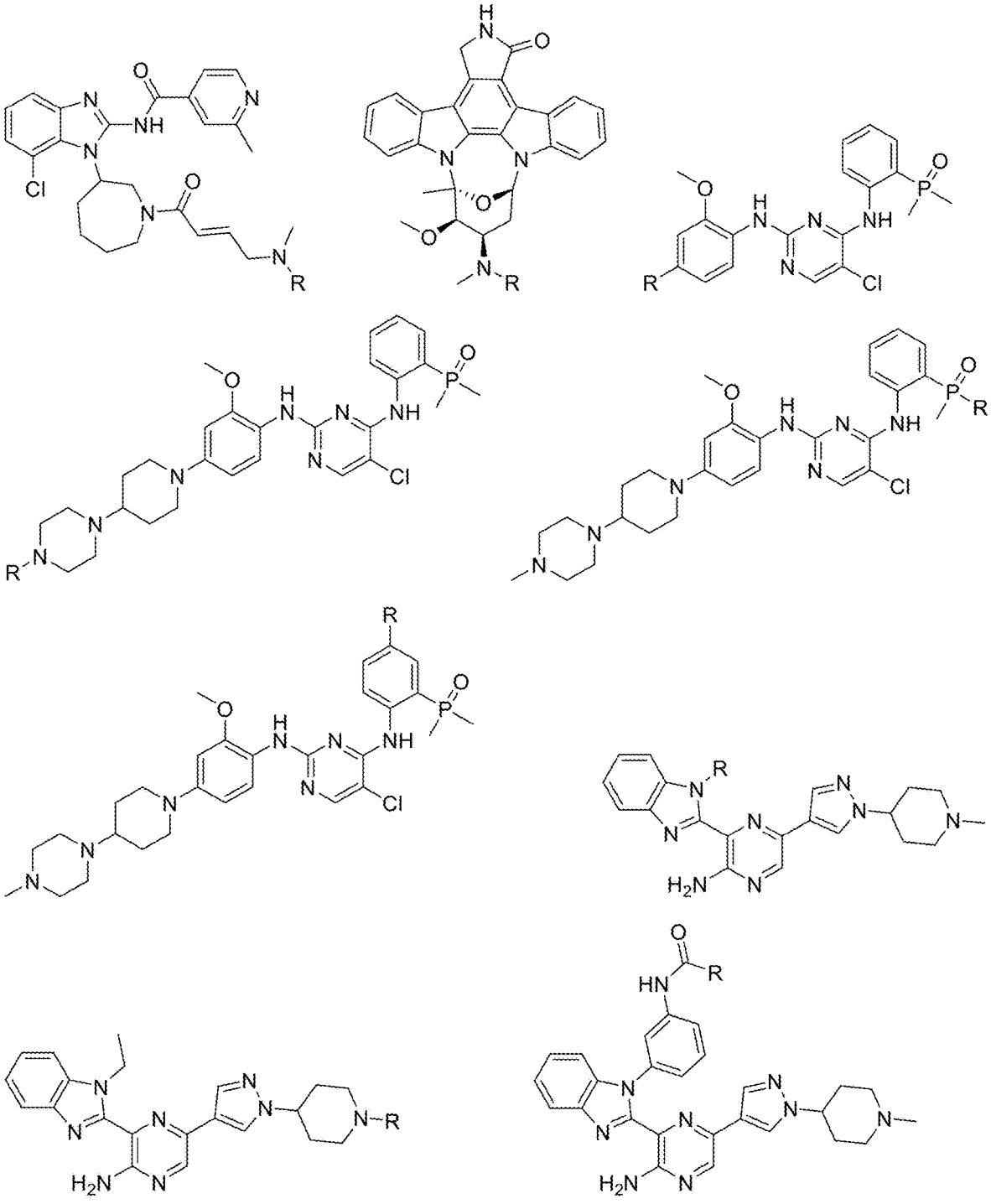


FIG. 8SS

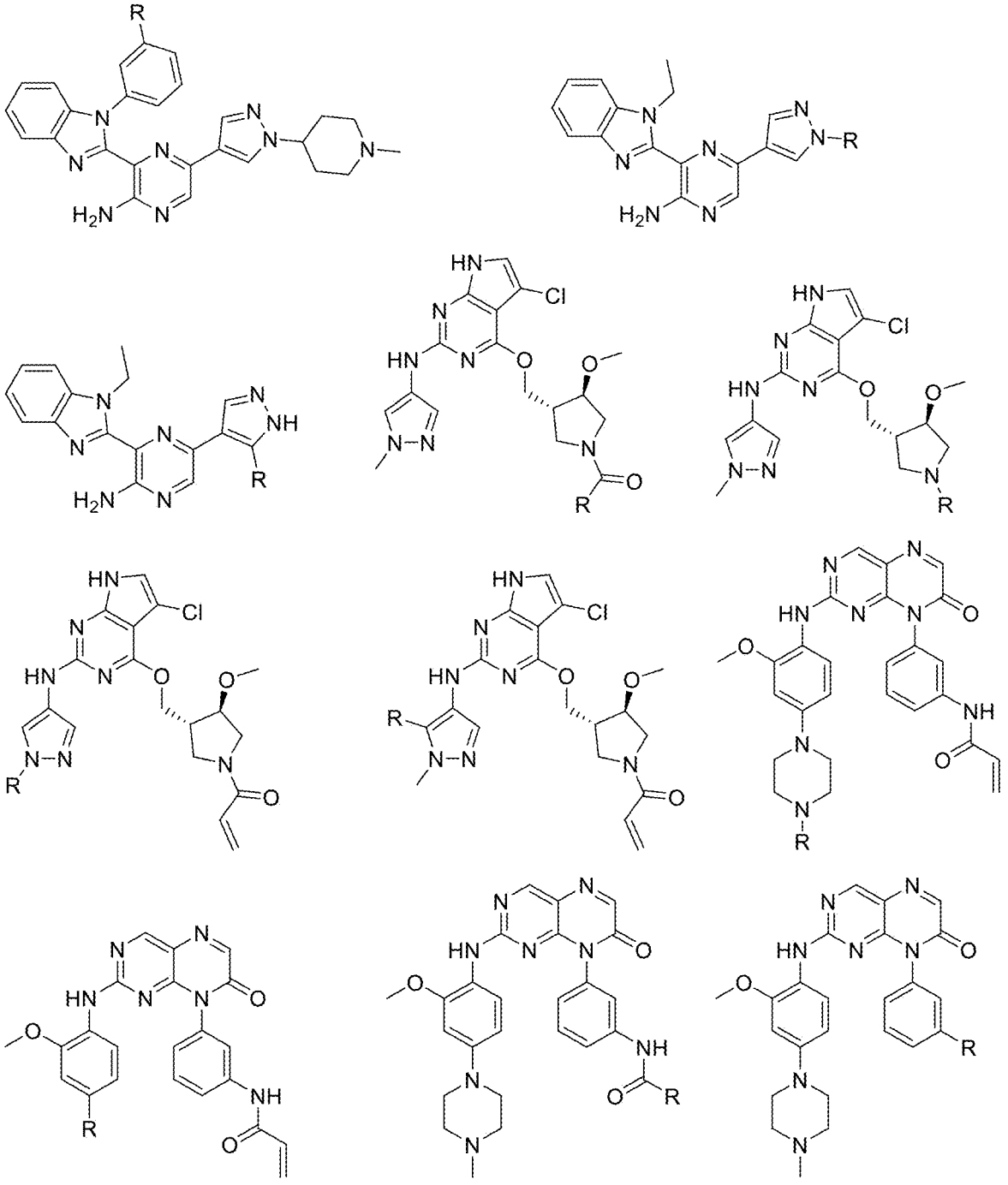


FIG. 8TT

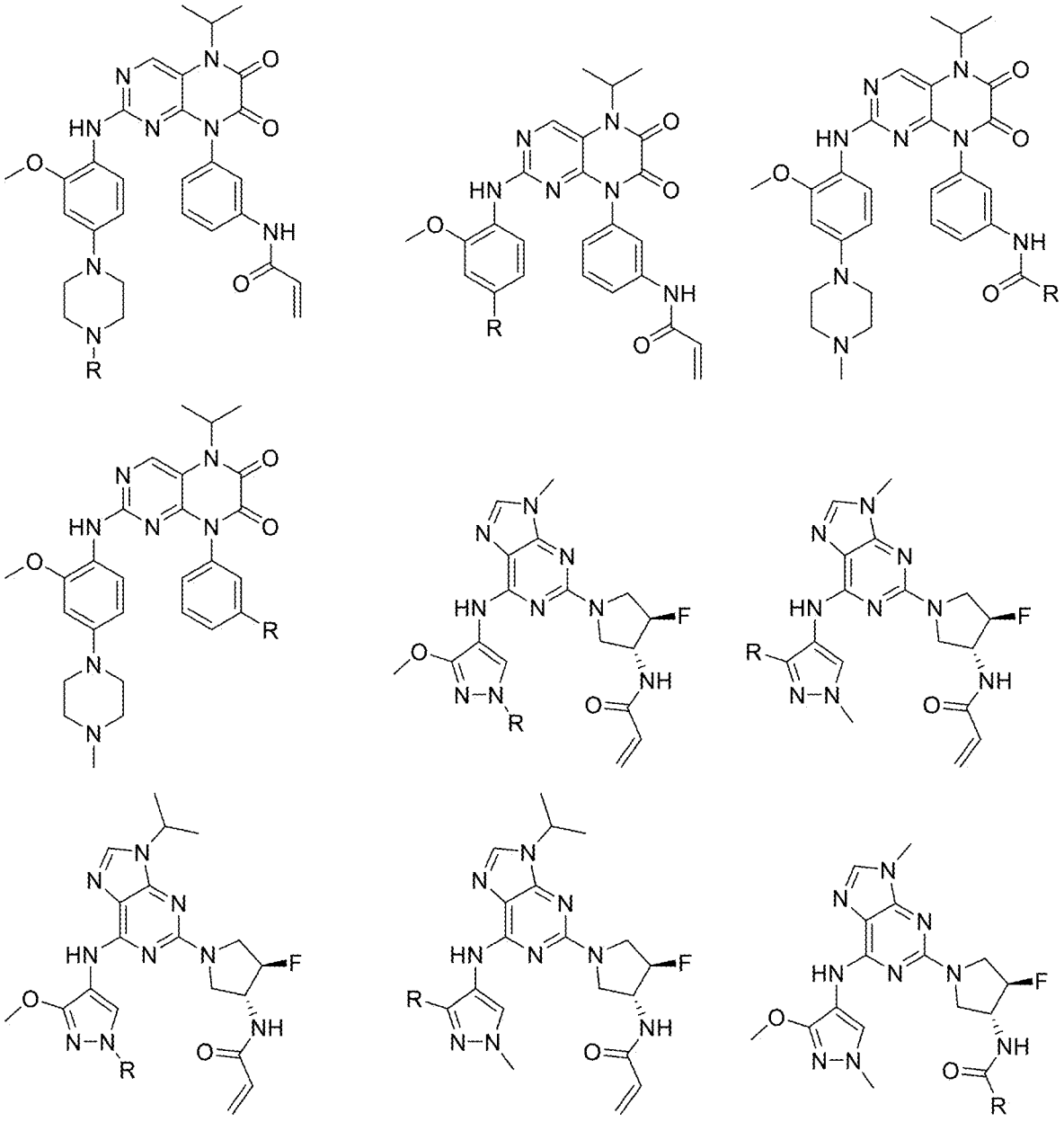


FIG. 8UU

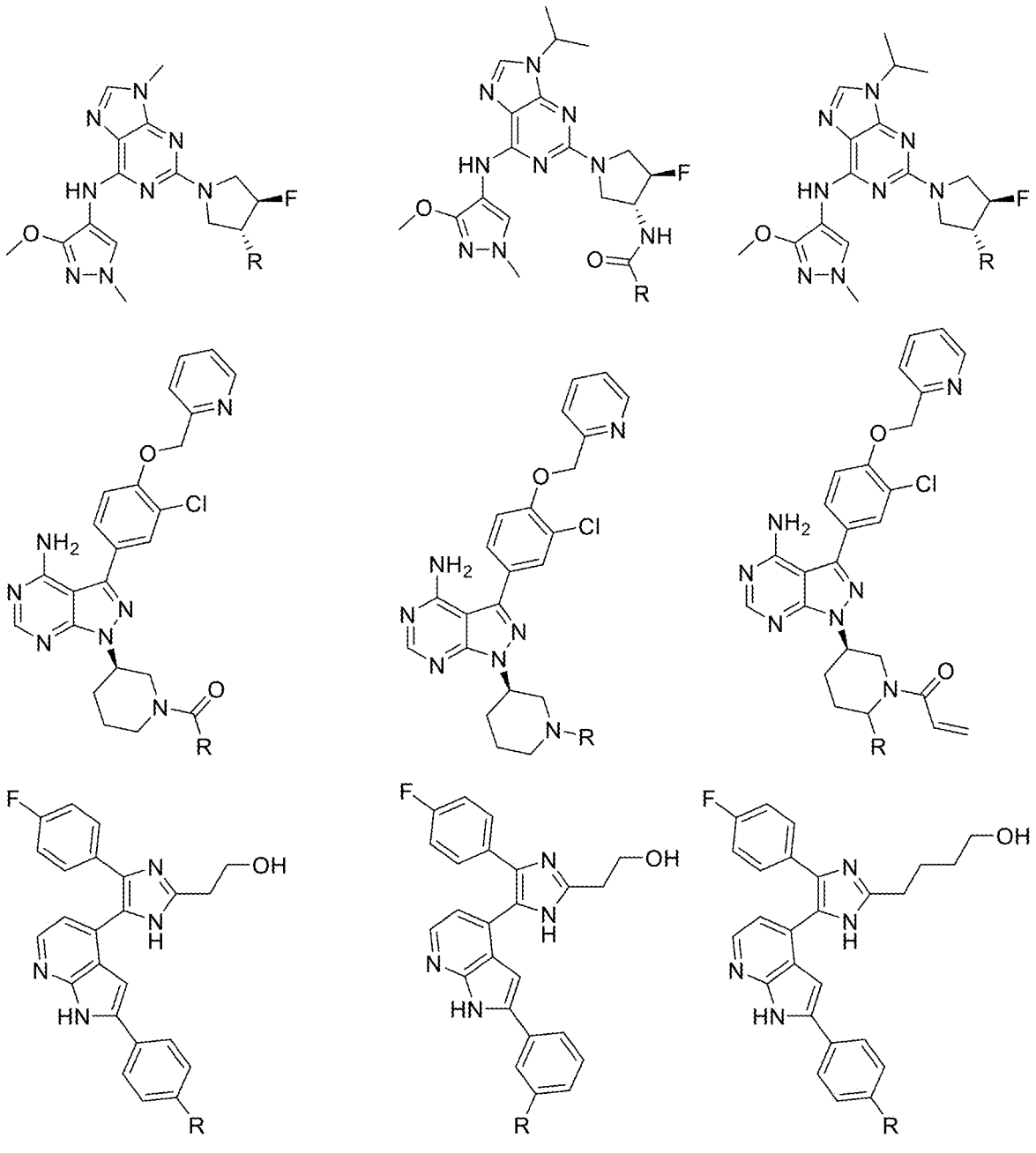


FIG. 8VV

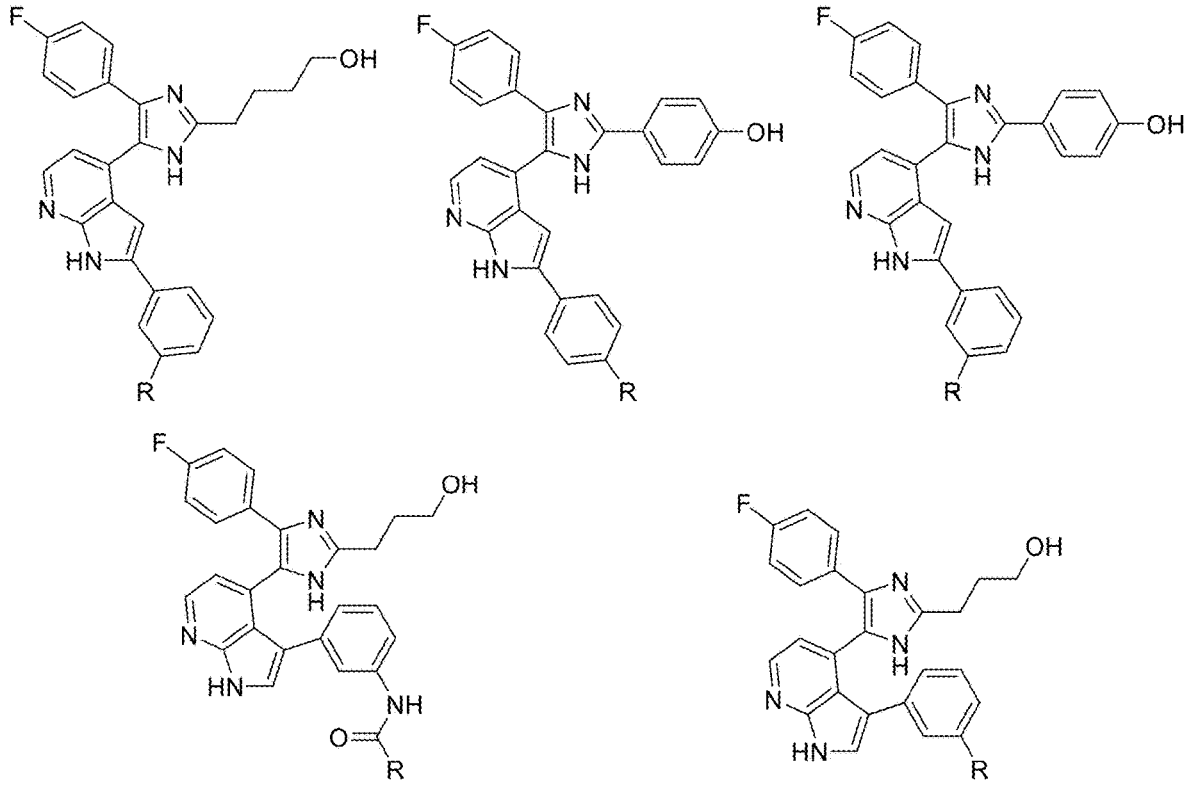


FIG. 8WW

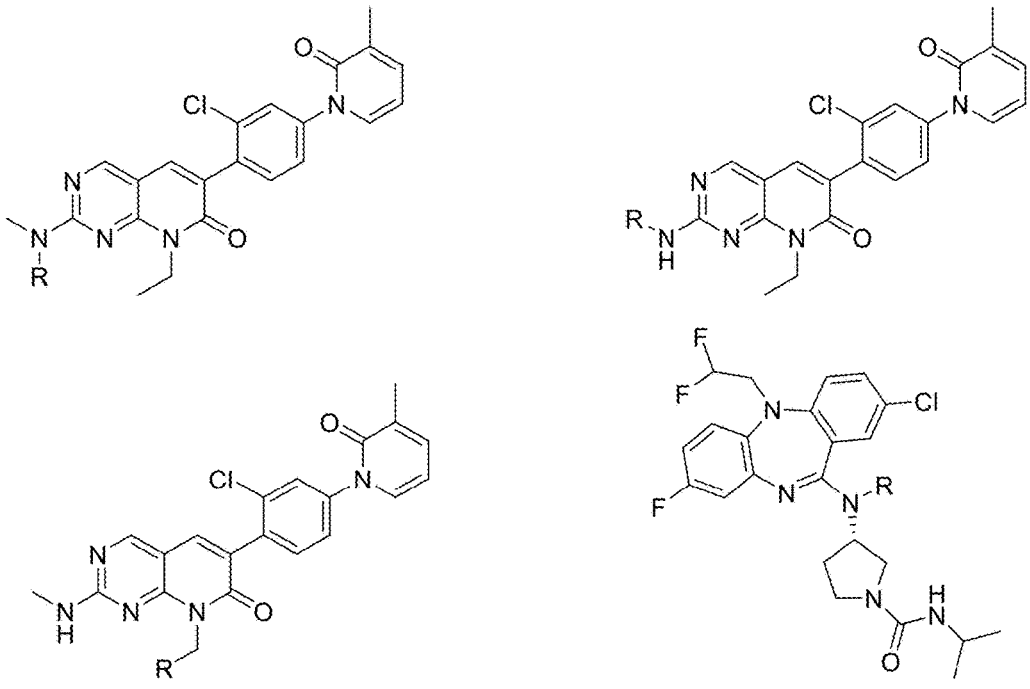


FIG. 8XX

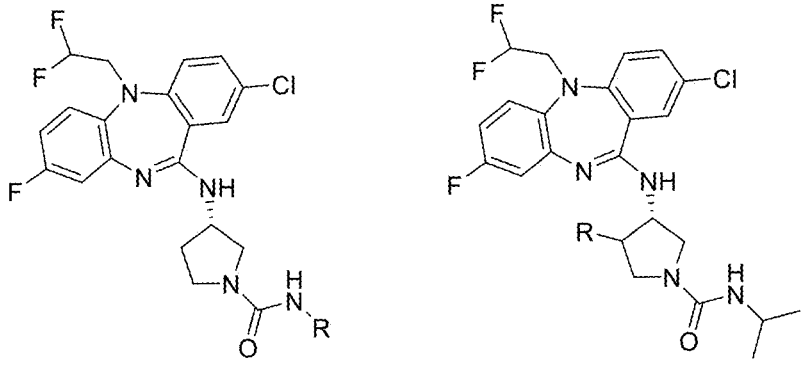


FIG. 8YY

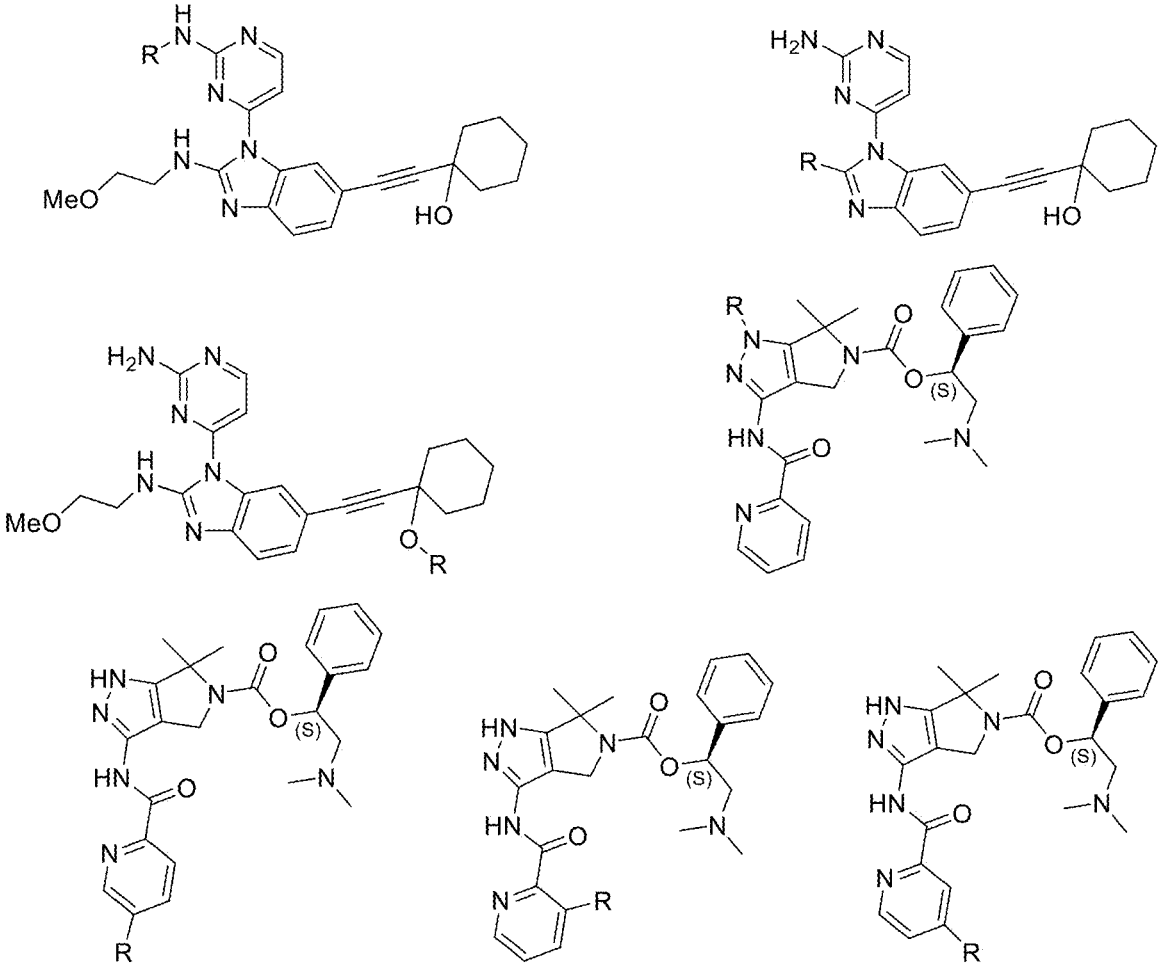


FIG. 8ZZ

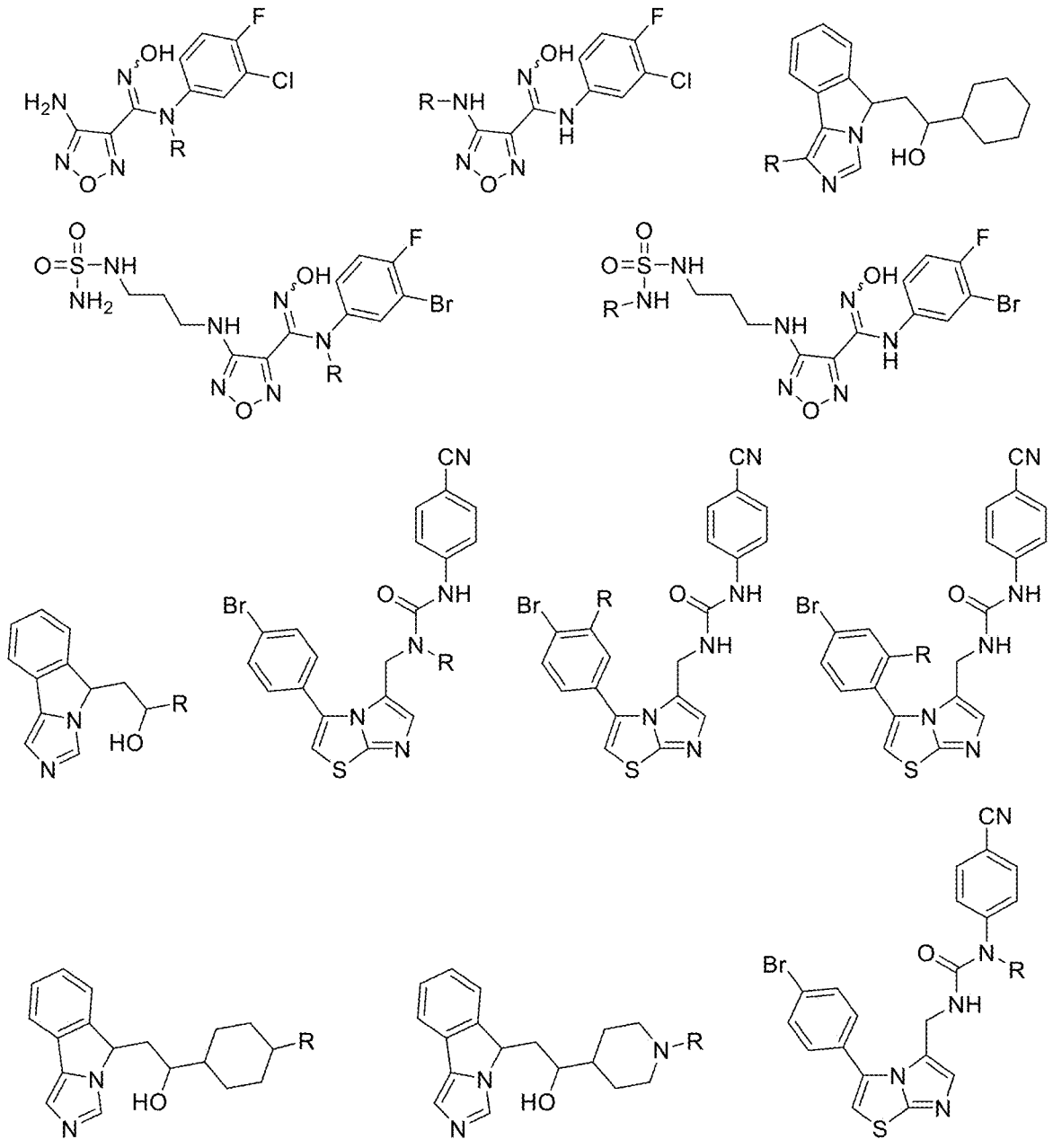


FIG. 8AAA

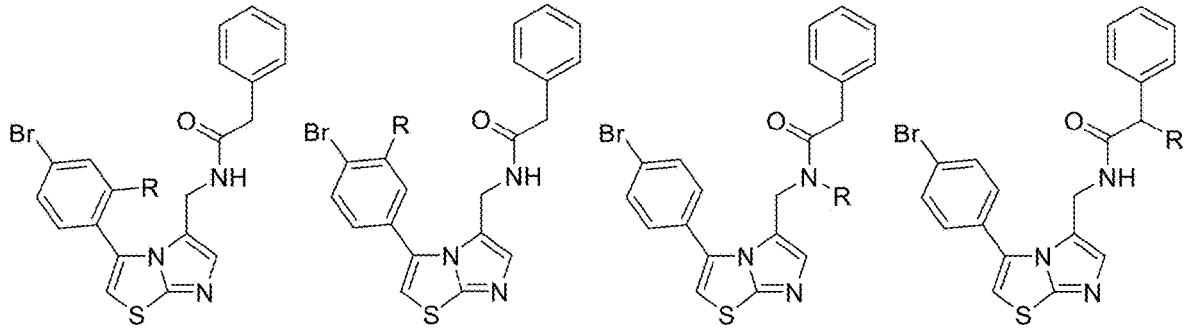


FIG. 8BBB

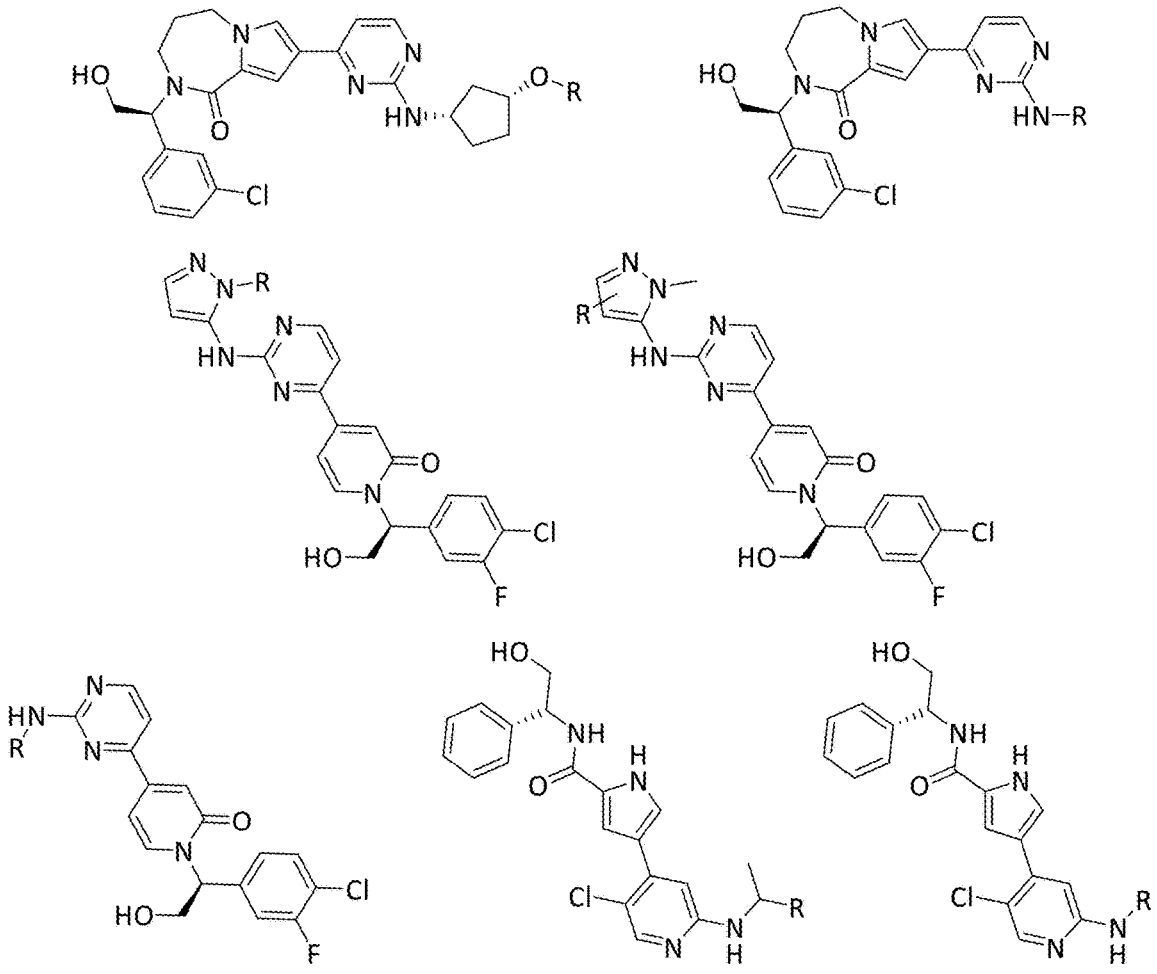


FIG. 8CCC

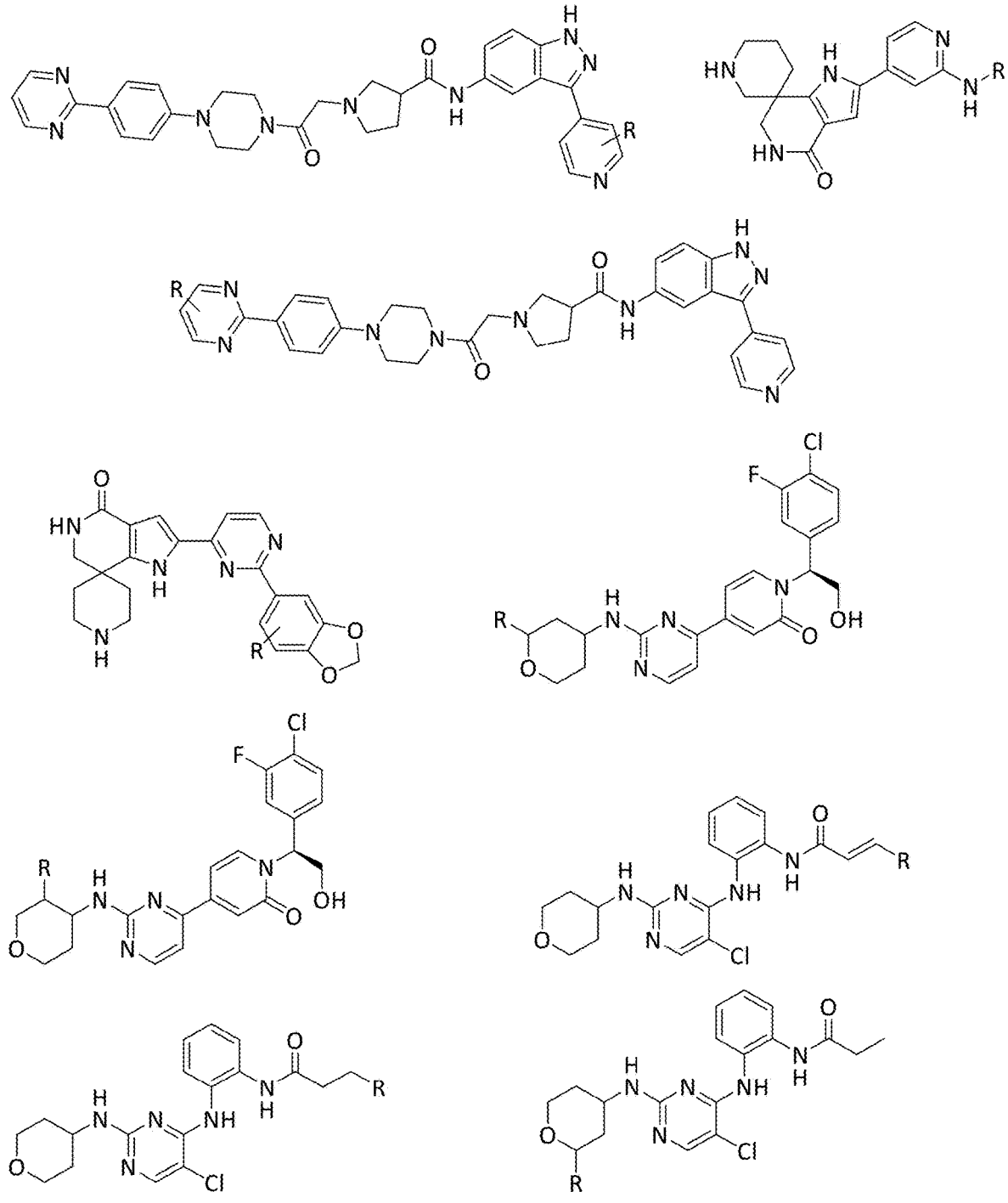


FIG. 8DDD

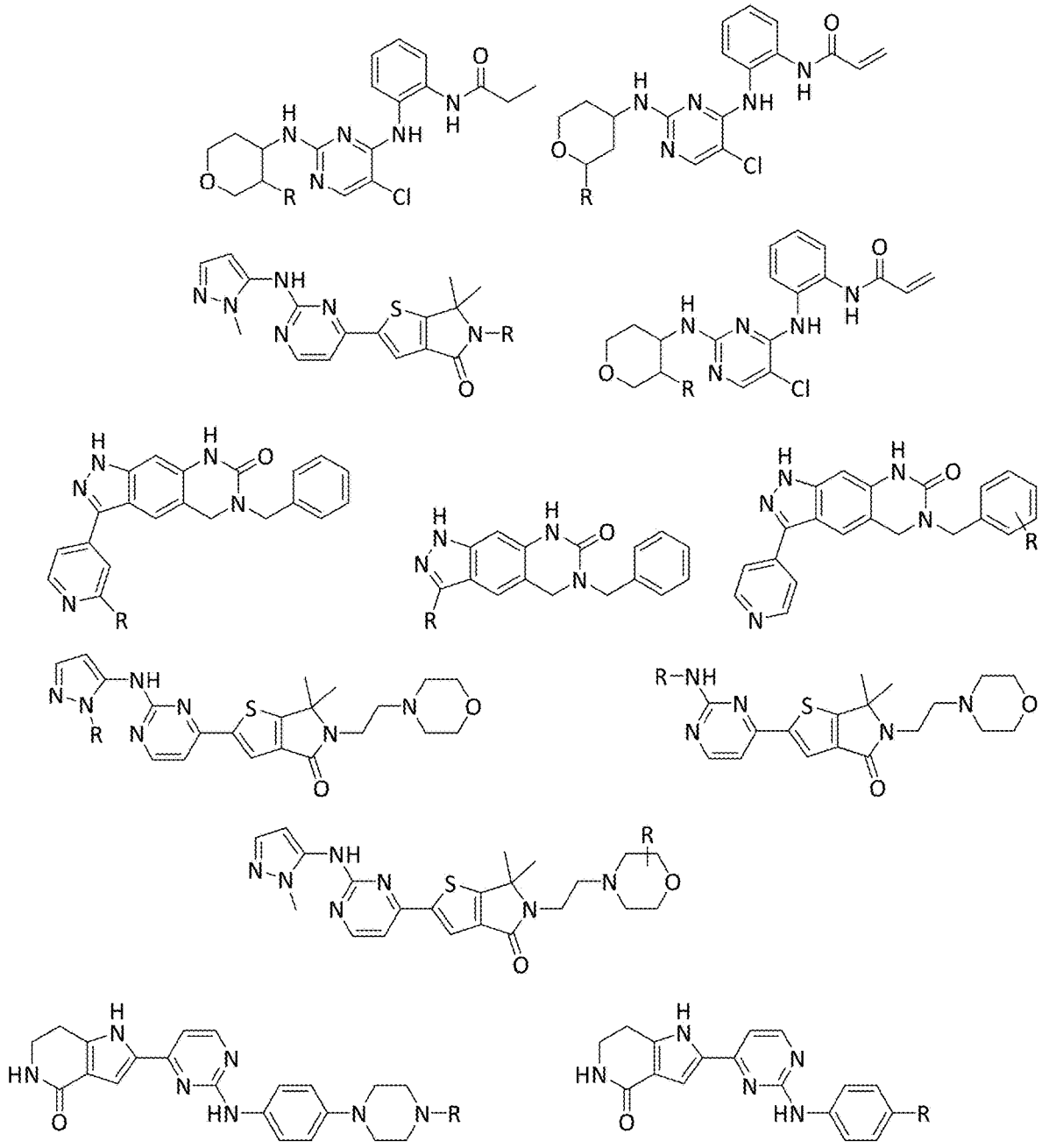


FIG. 8EEE

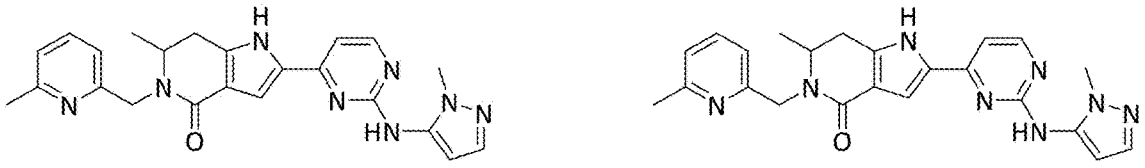


FIG. 8FFF

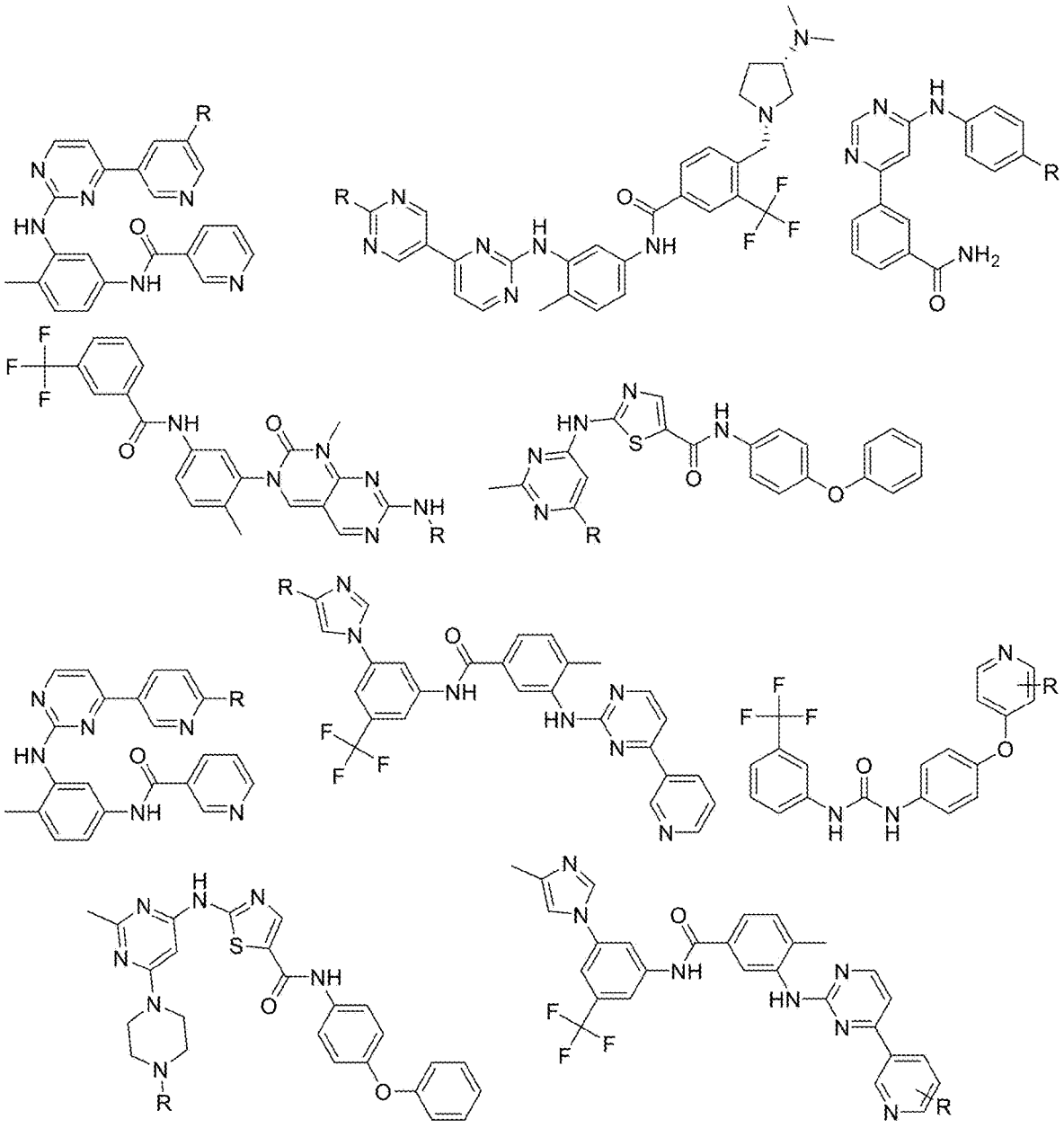


FIG. 8GGG

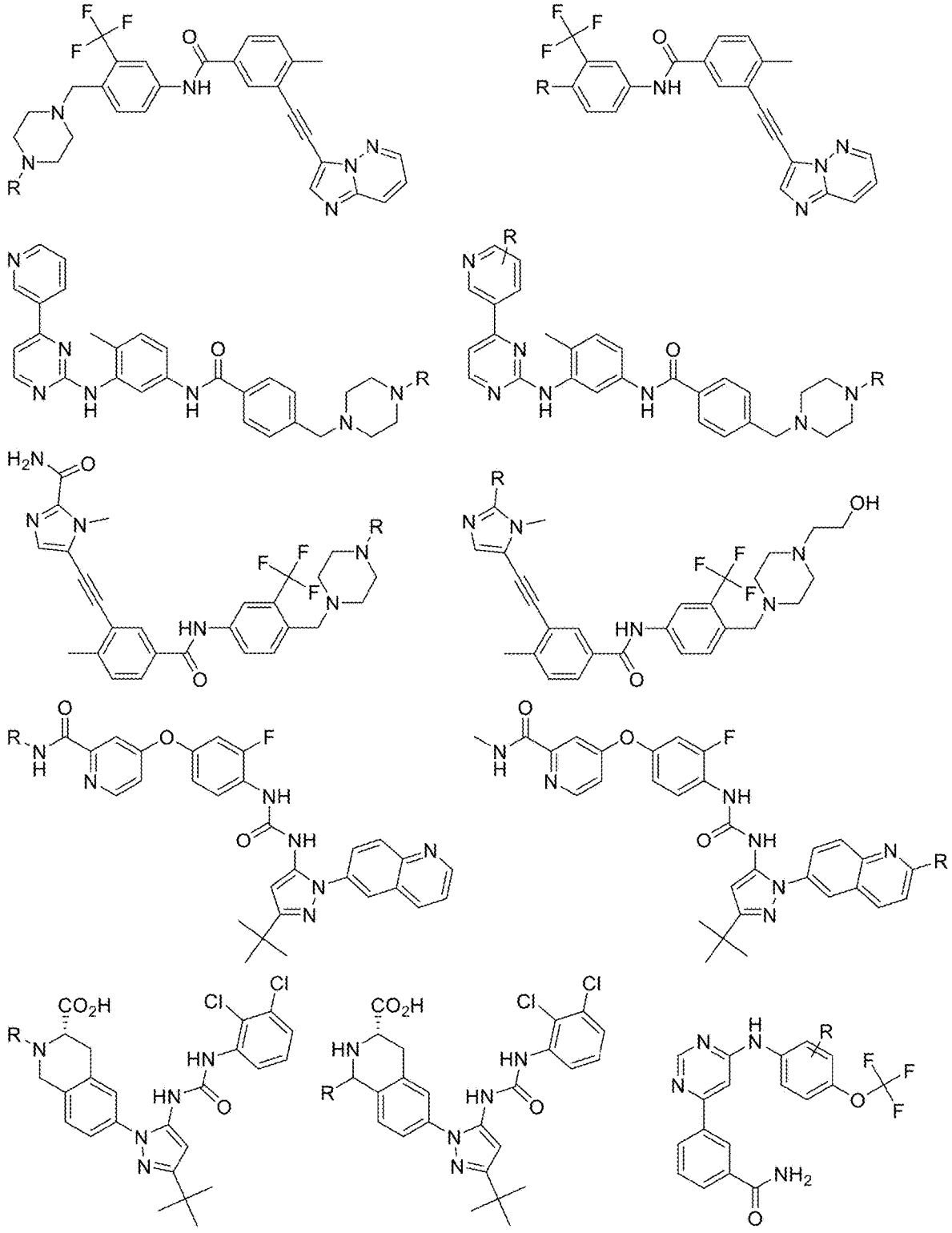


FIG. 8HHH

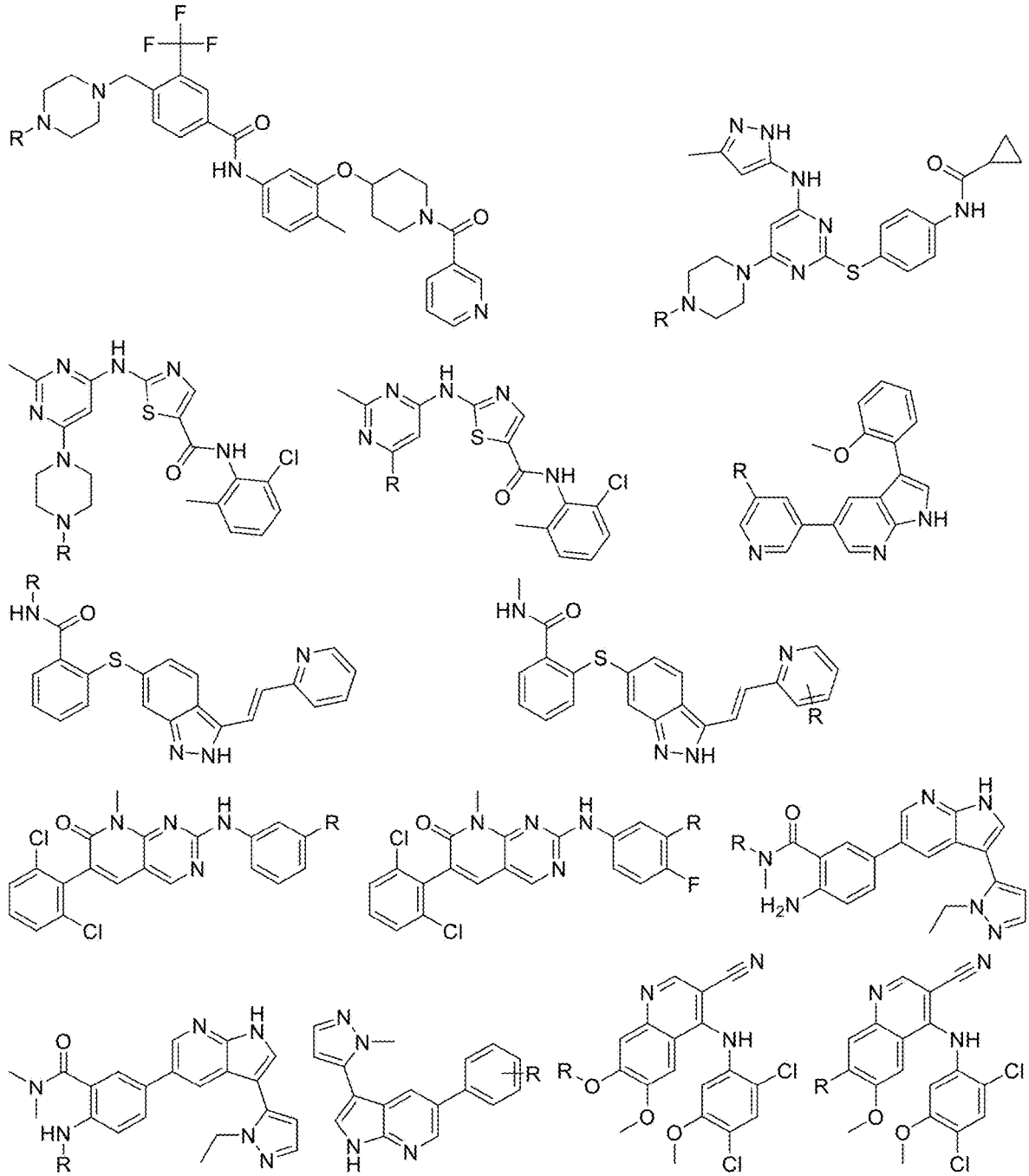


FIG. 8III

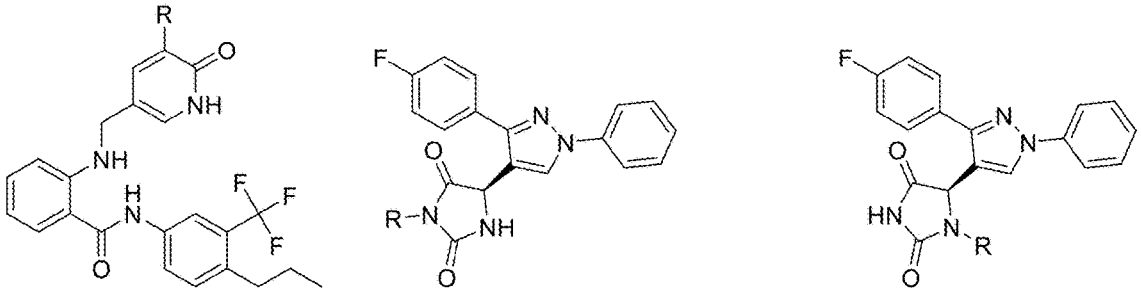


FIG. 8JJJ

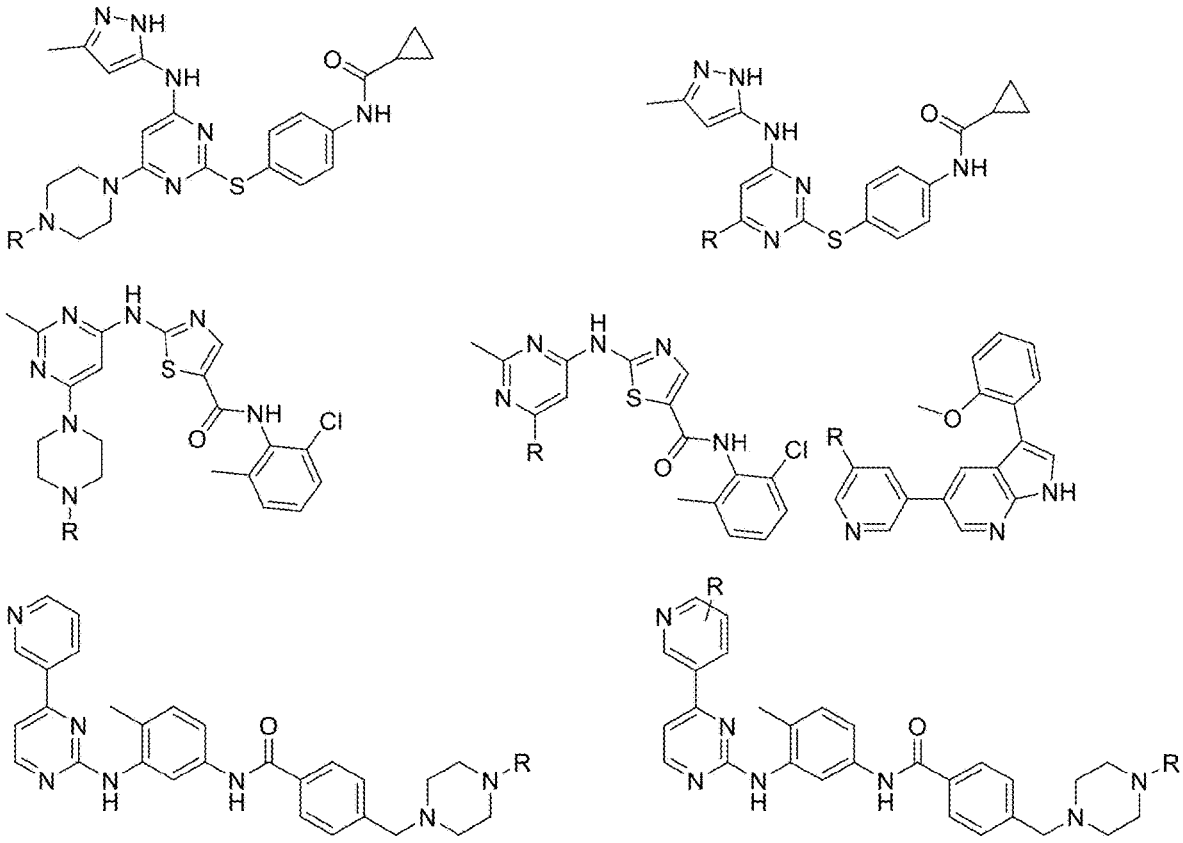


FIG. 8KKK

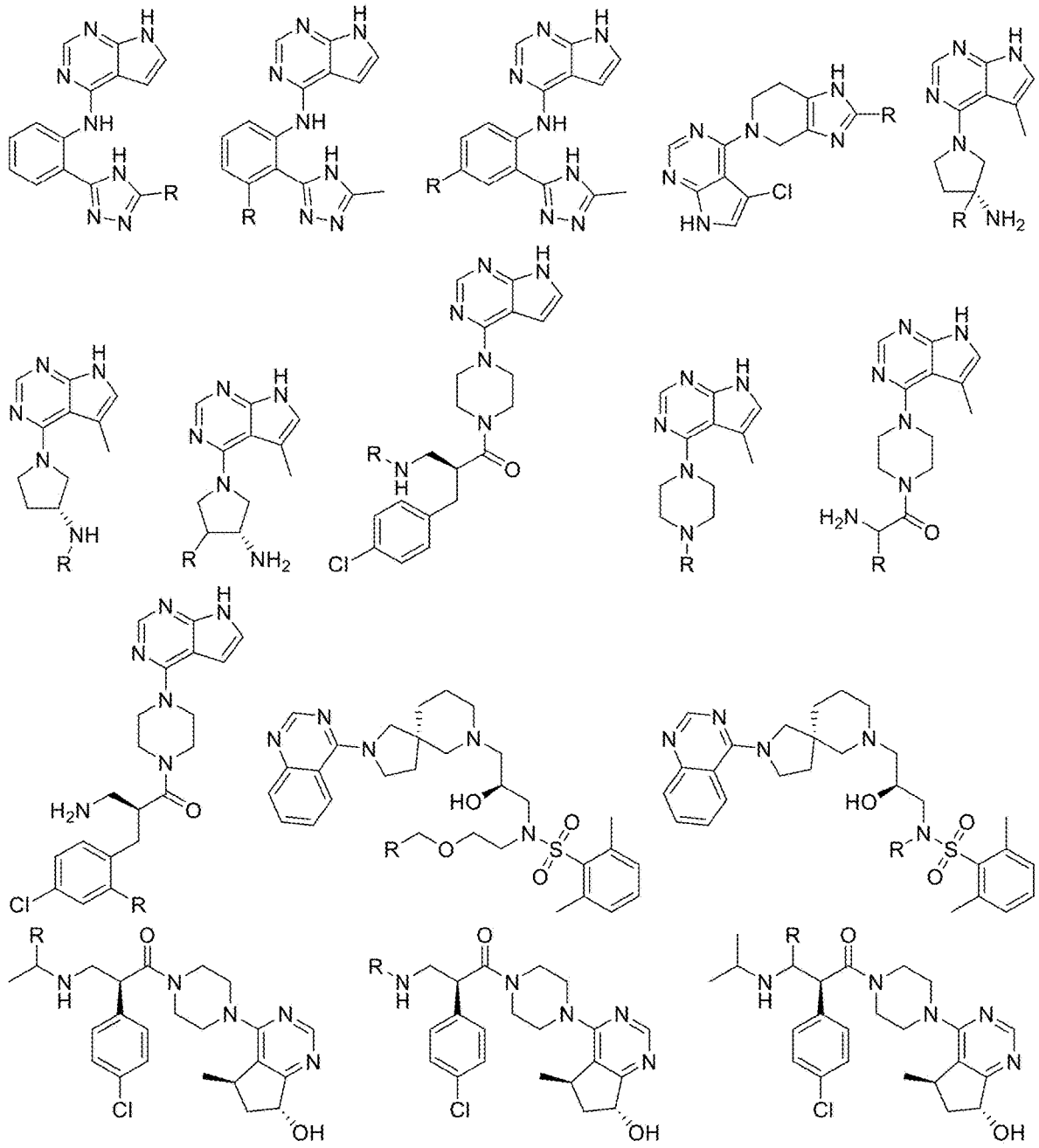


FIG. 8LLL

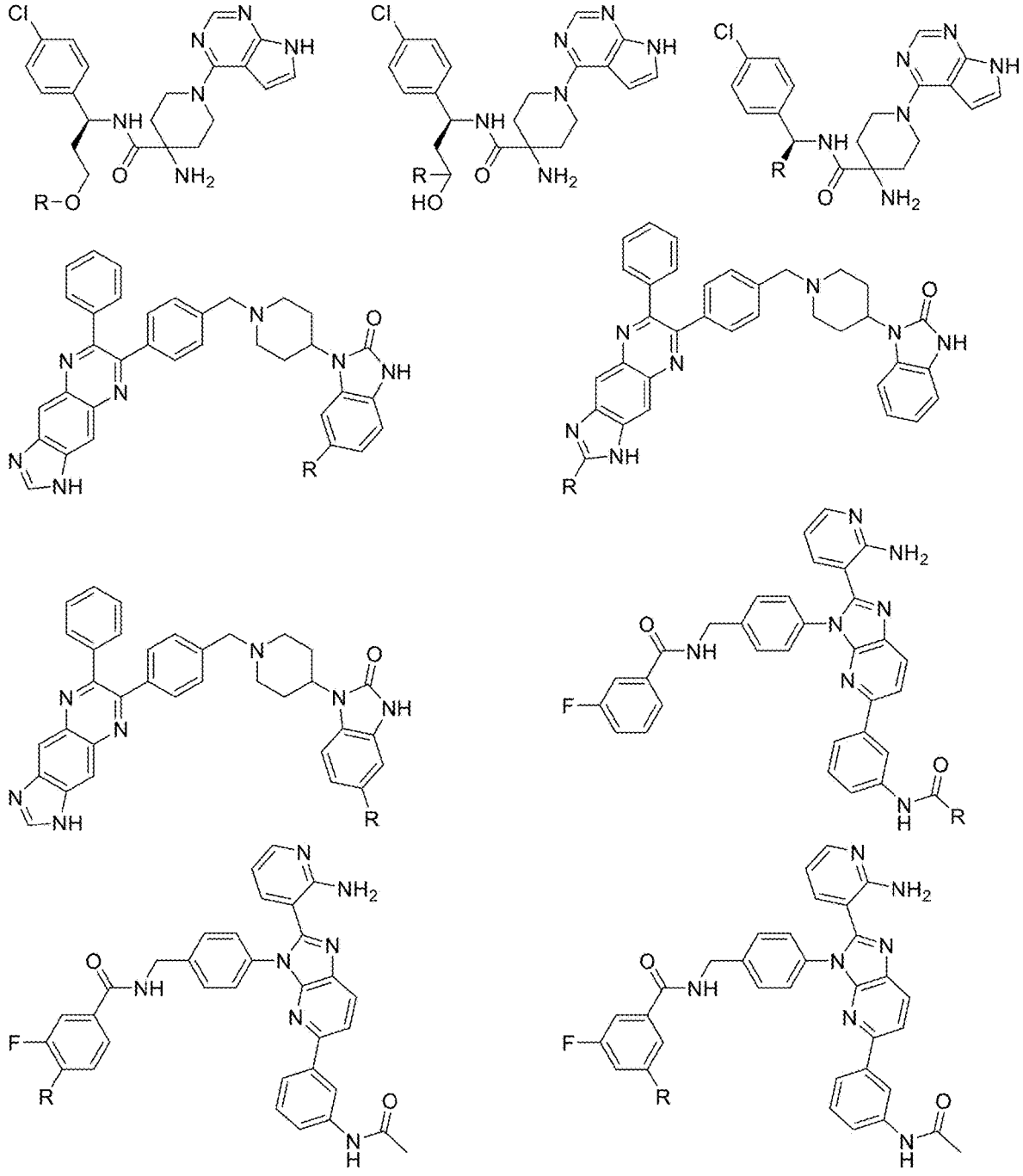


FIG. 8MMM

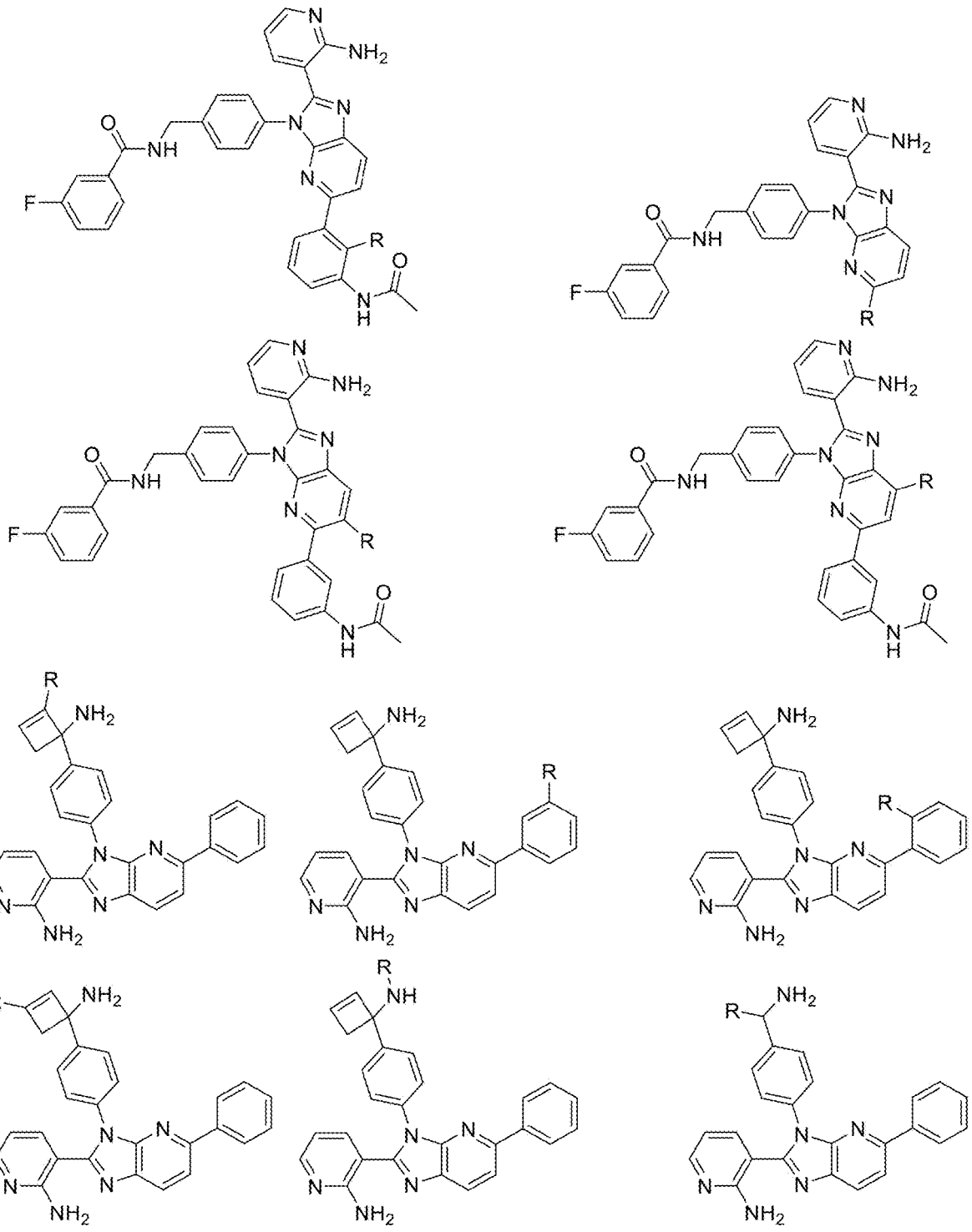


FIG. 8NNN

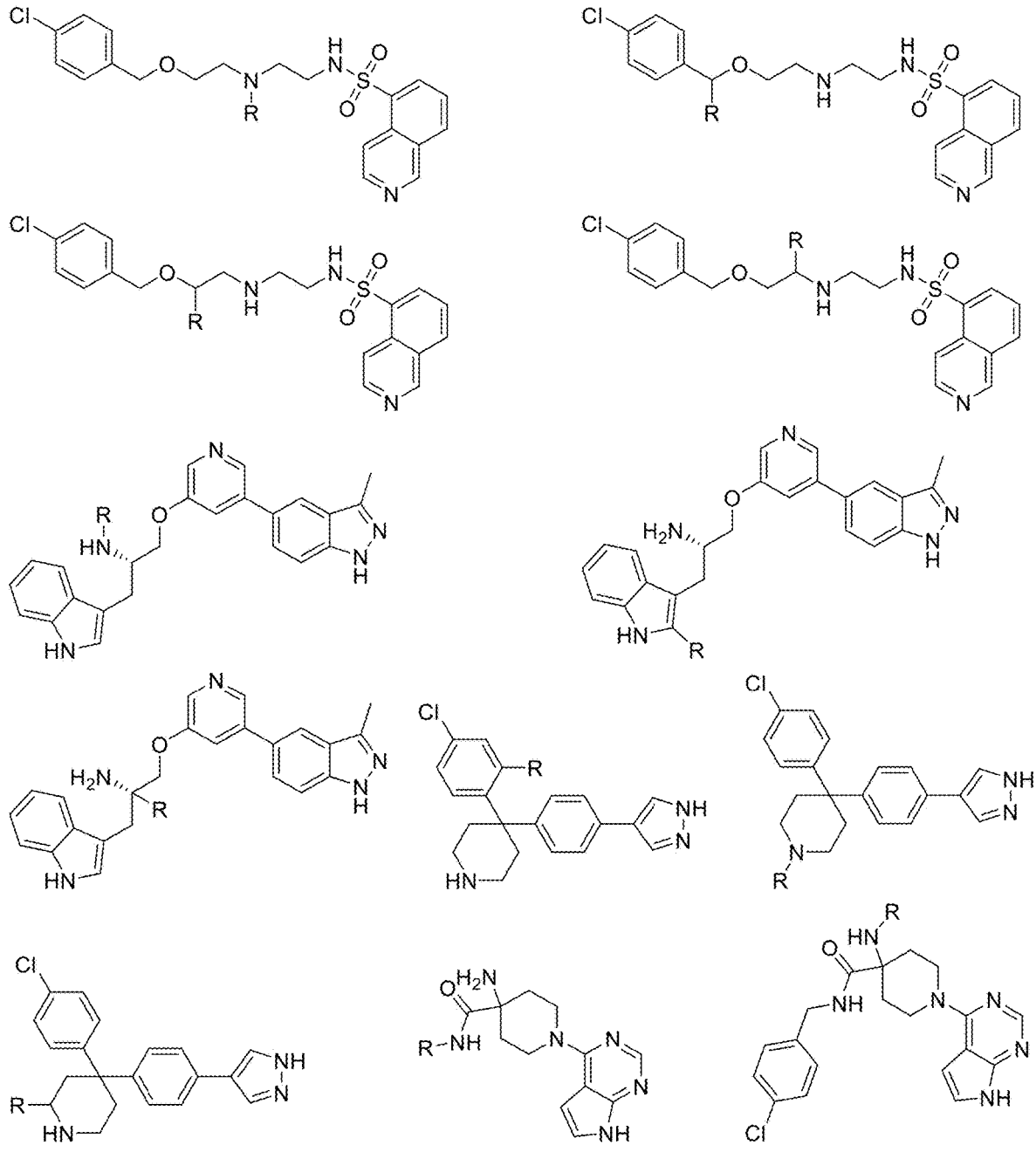


FIG. 8OOO

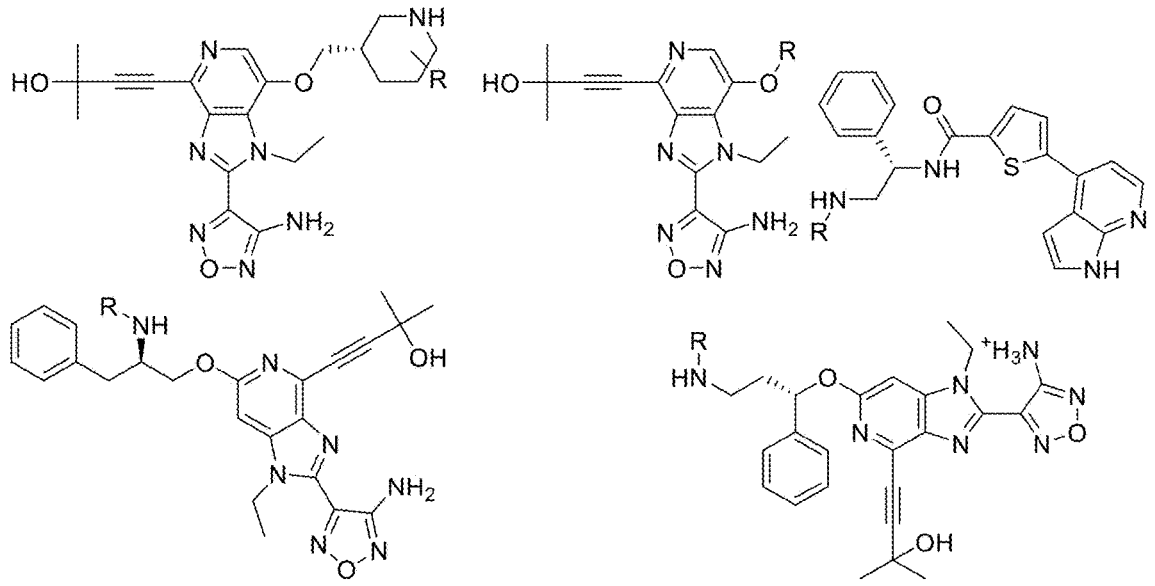


FIG. 8PPP

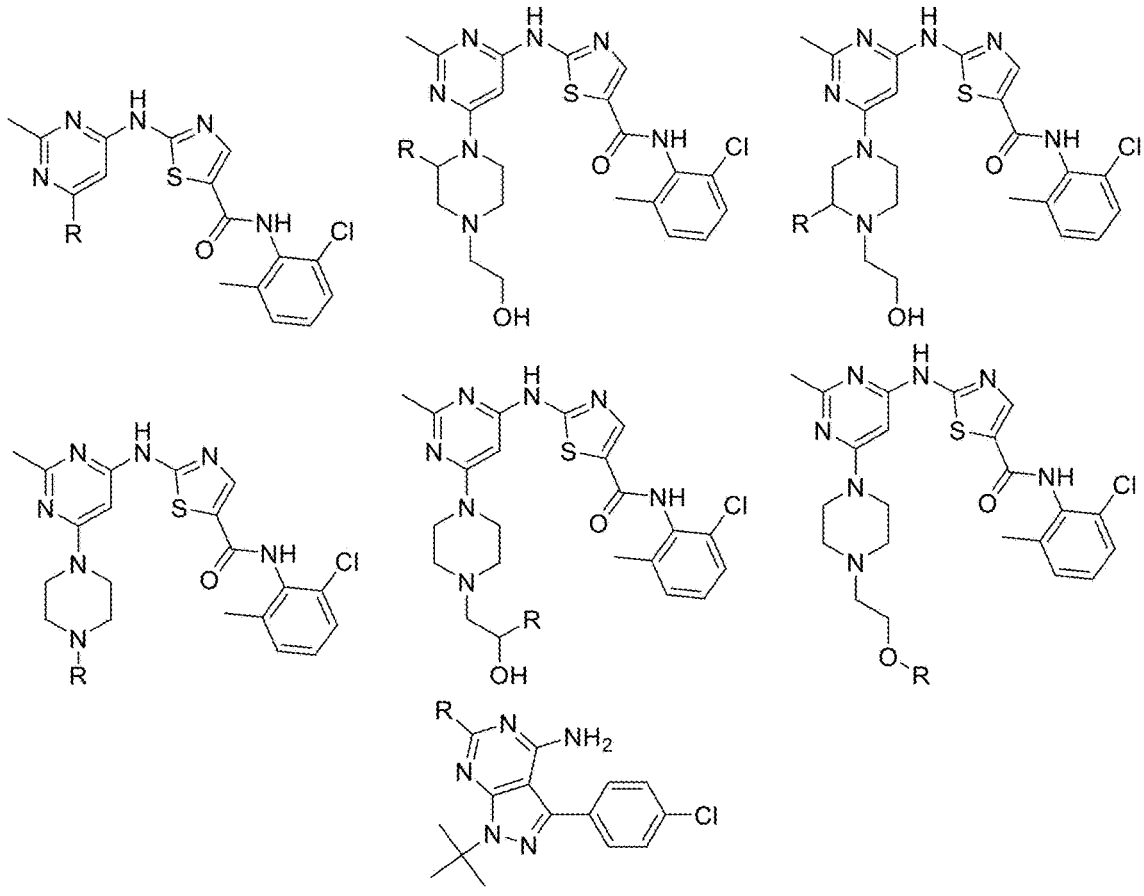


FIG. 8QQQ

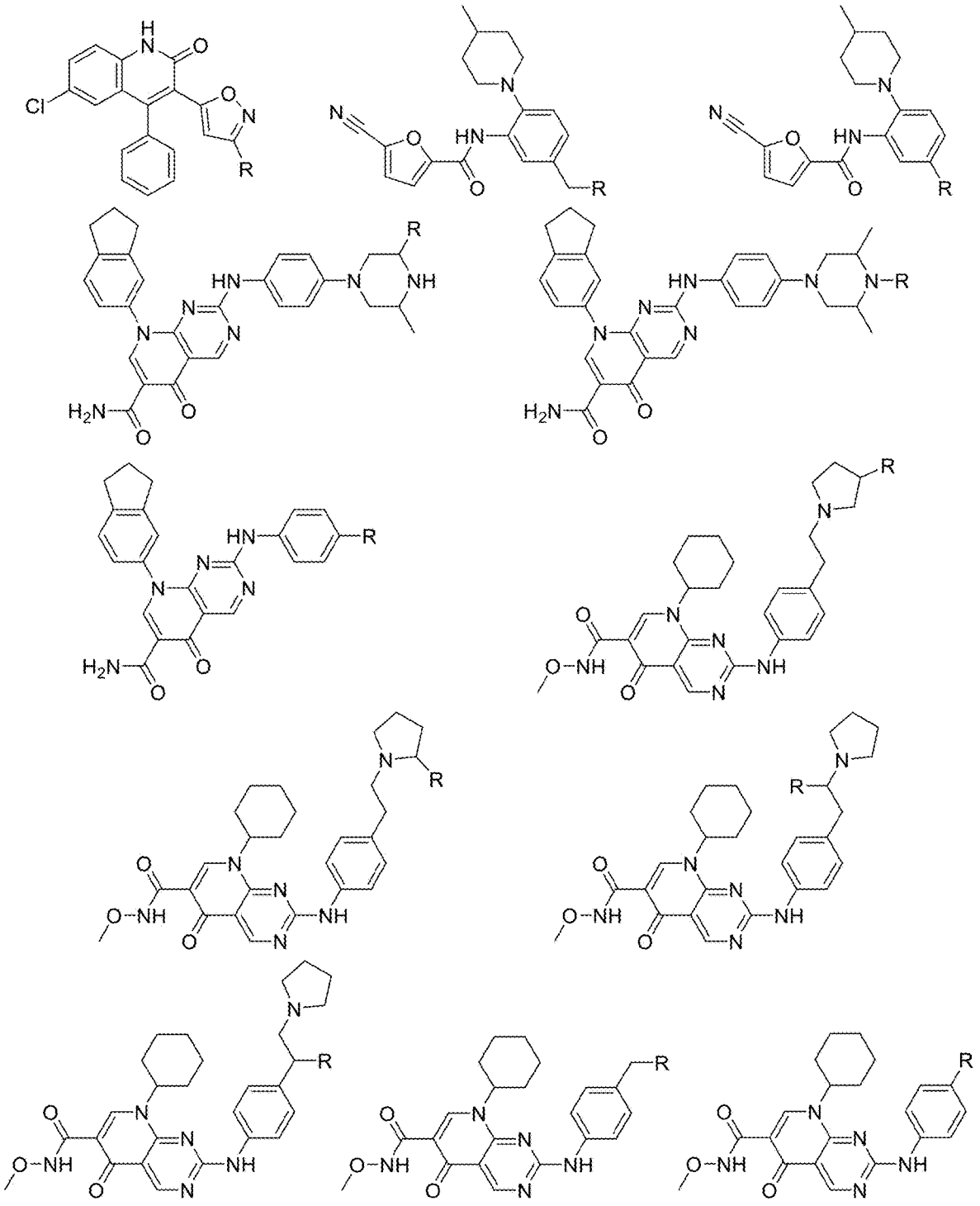


FIG. 8RRR

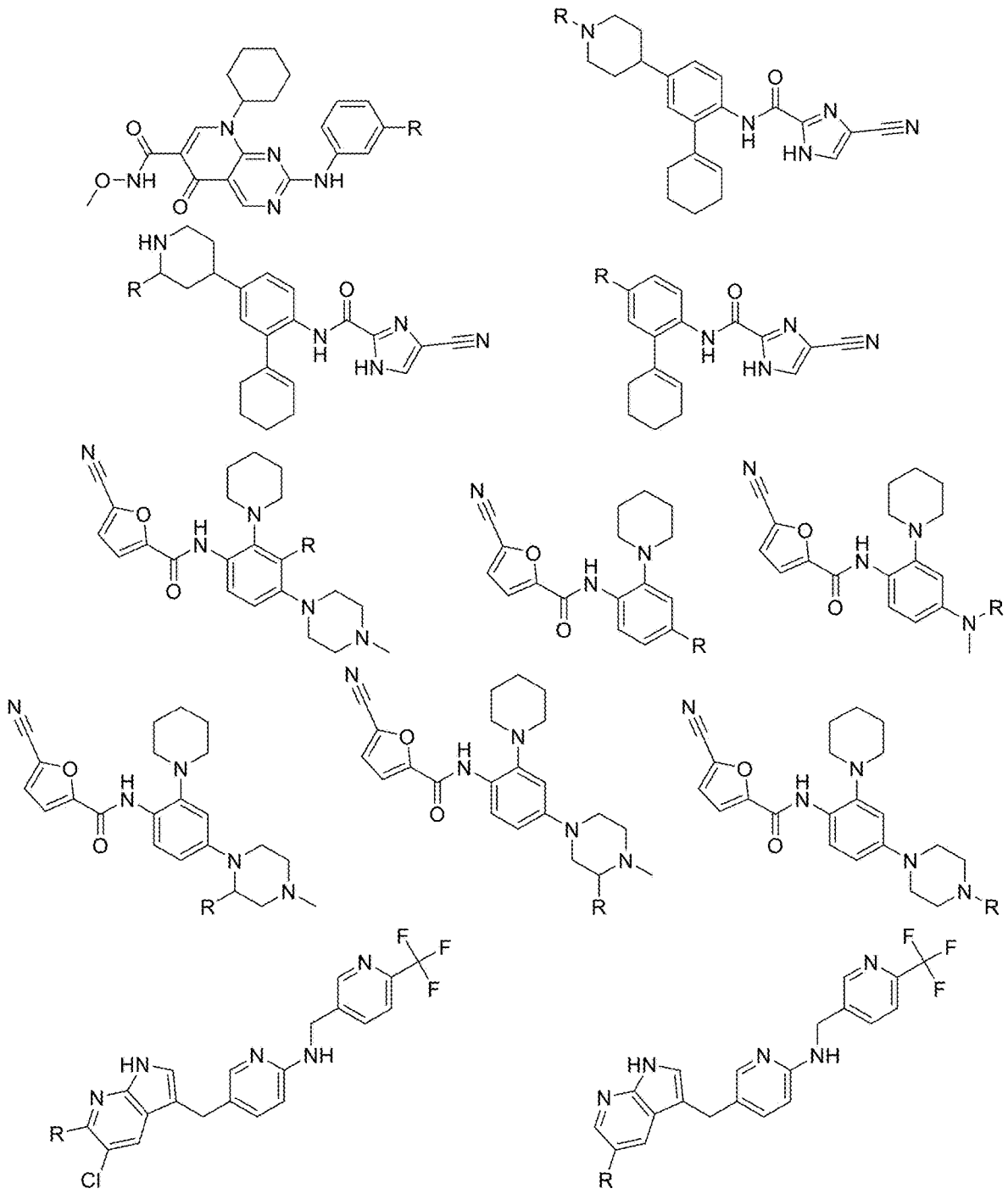


FIG. 8SSS

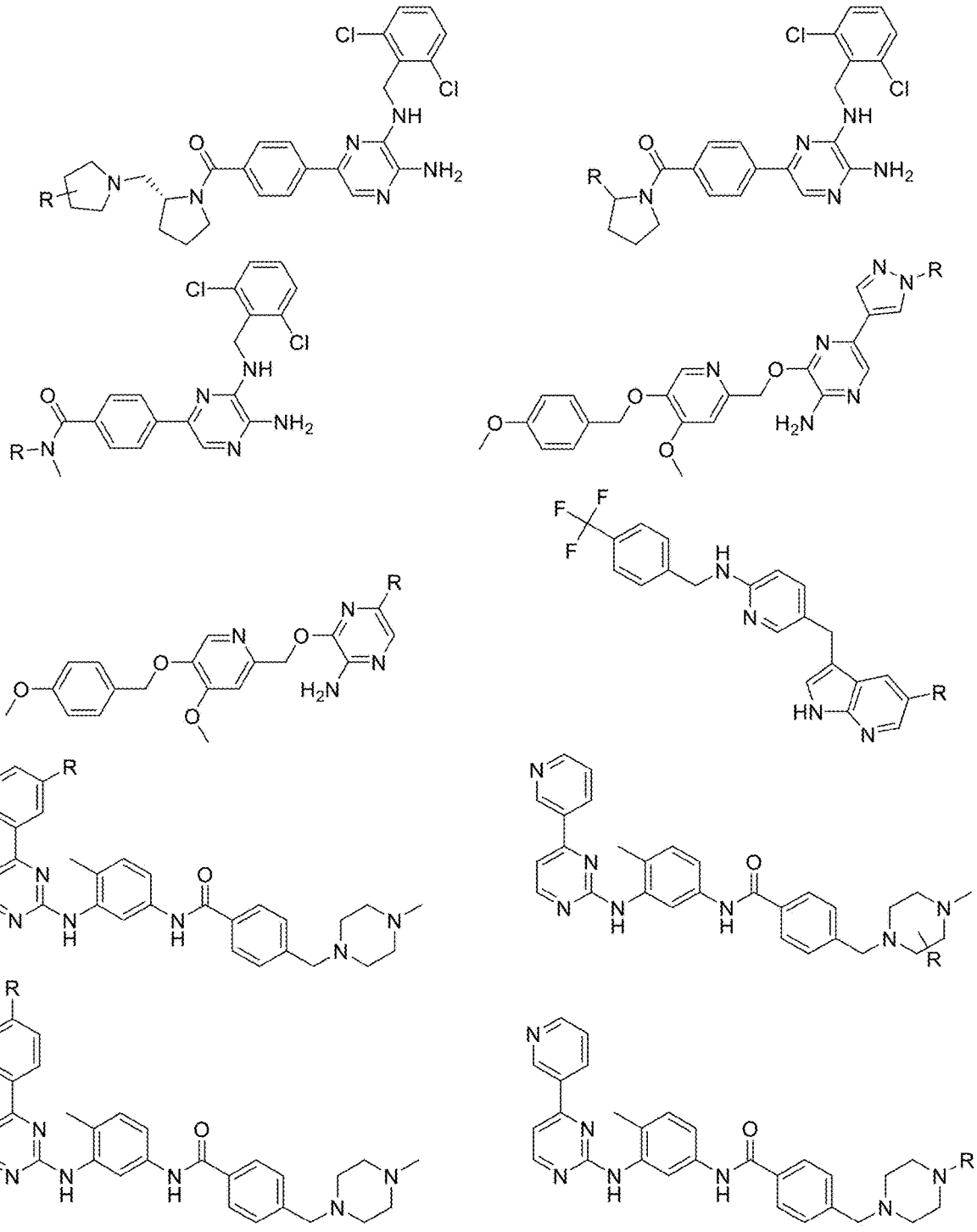


FIG. 8TTT

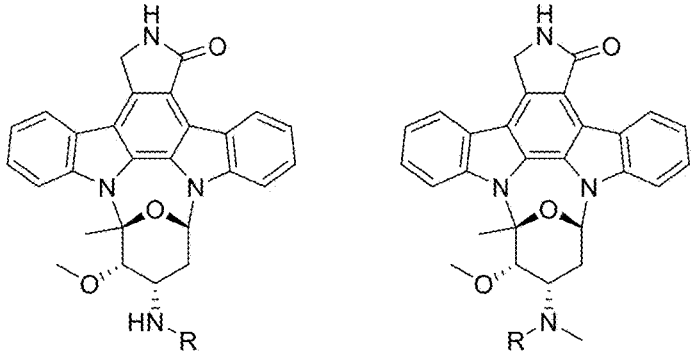


FIG. 8UUU

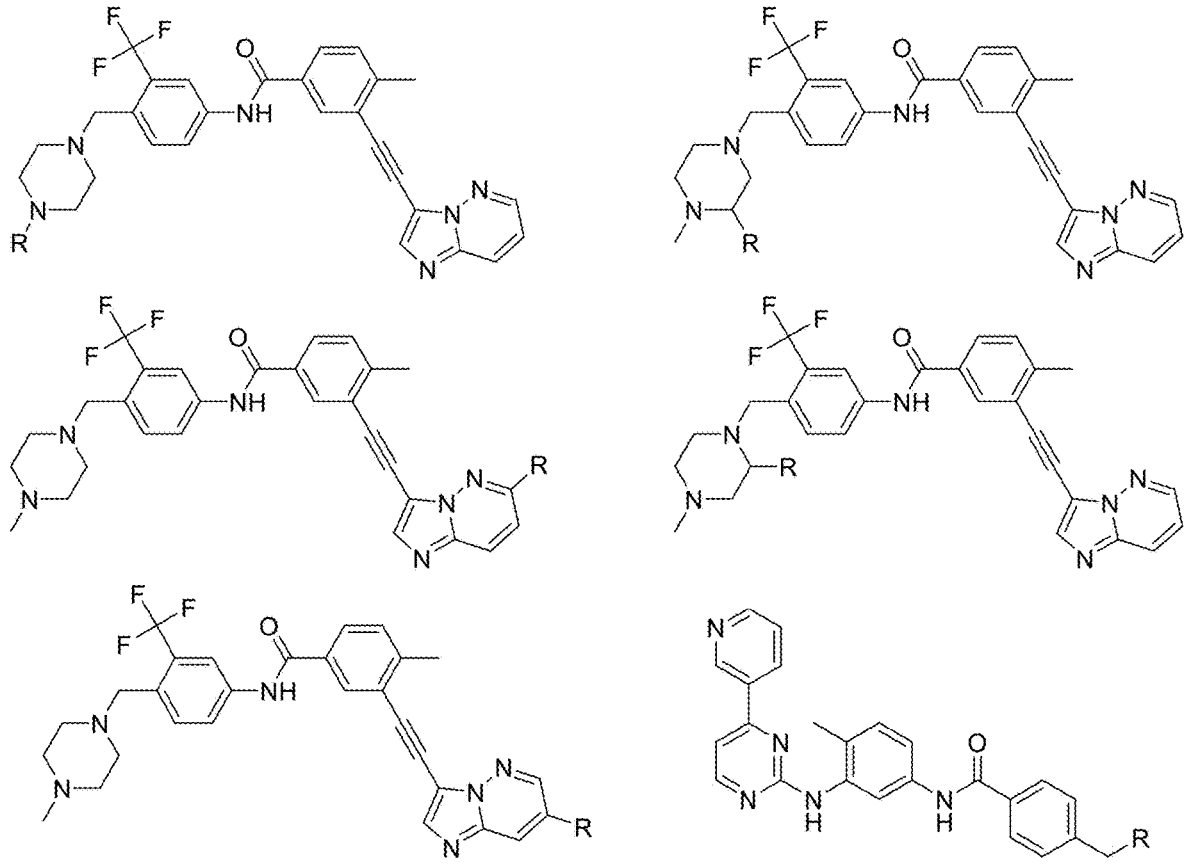


FIG. 8VVV

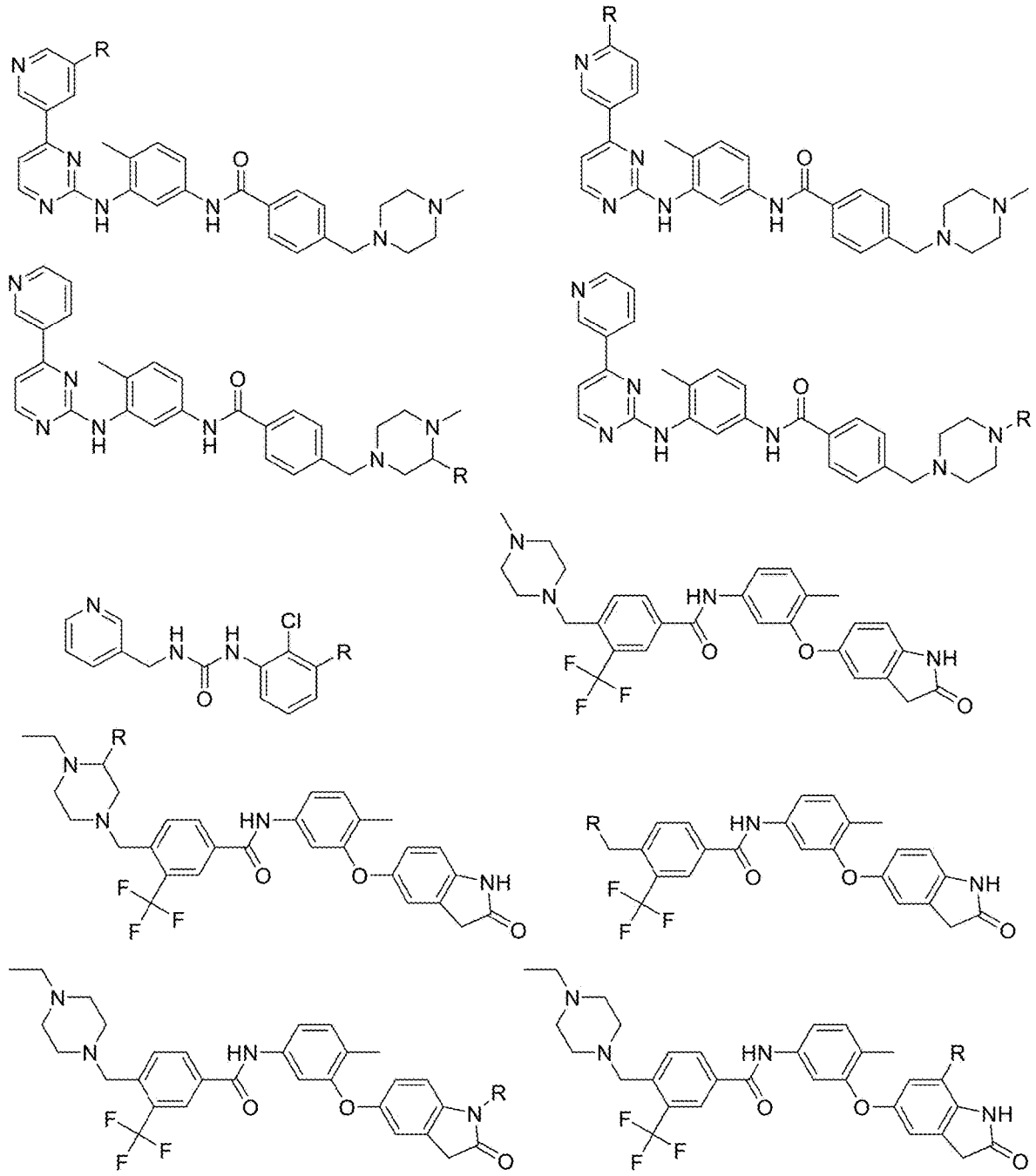


FIG. 8WWW

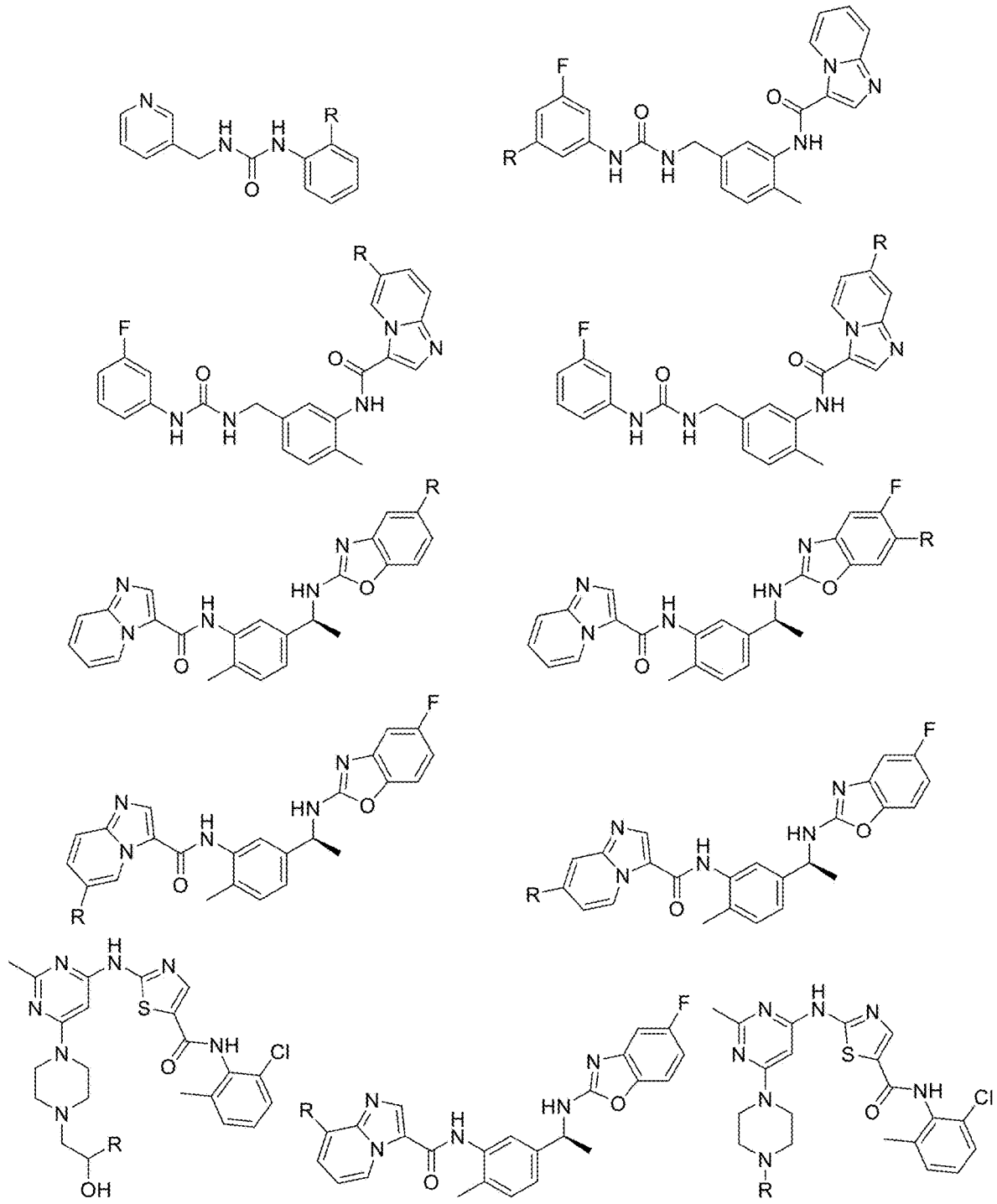


FIG. 8XXX

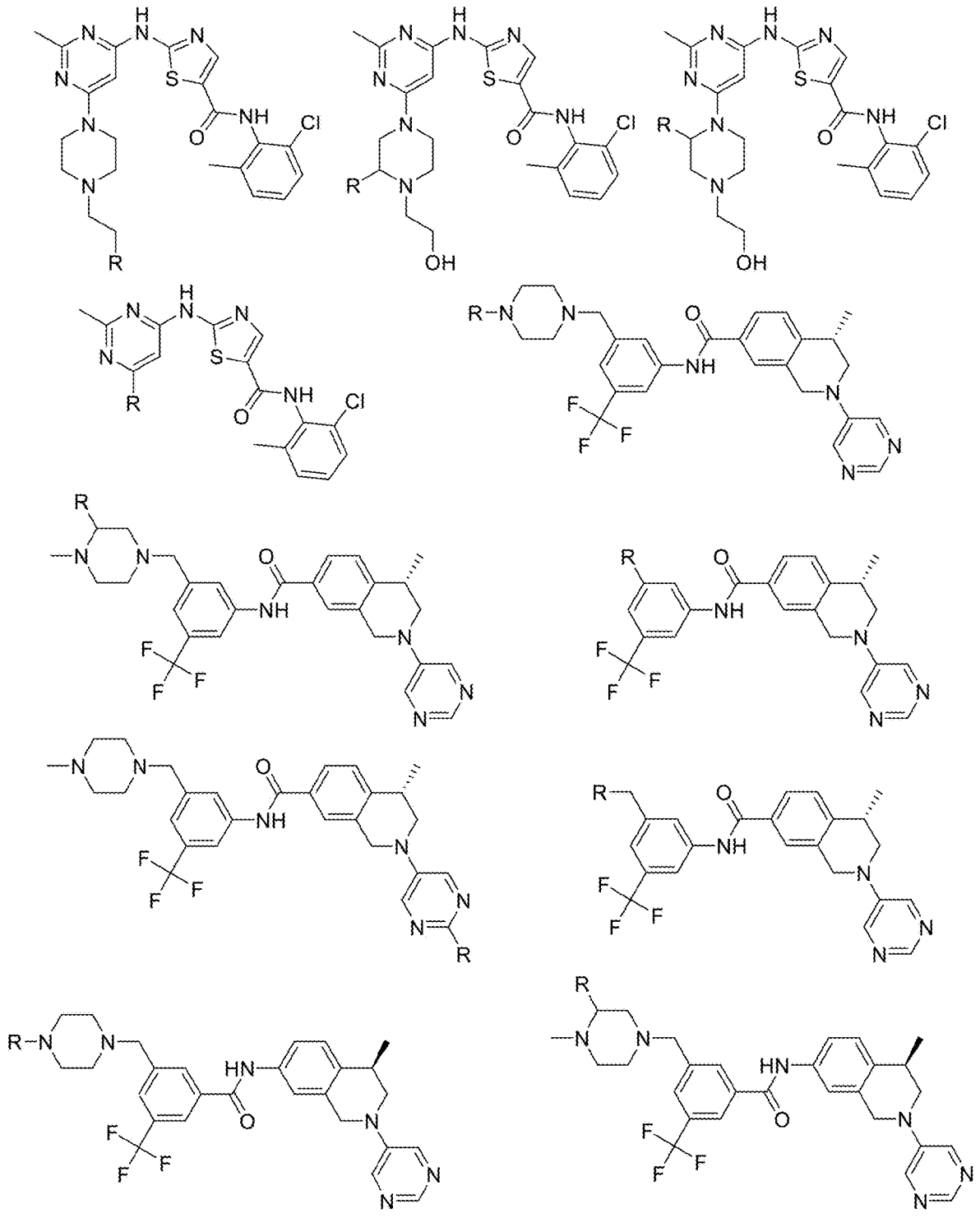


FIG. 8YYY

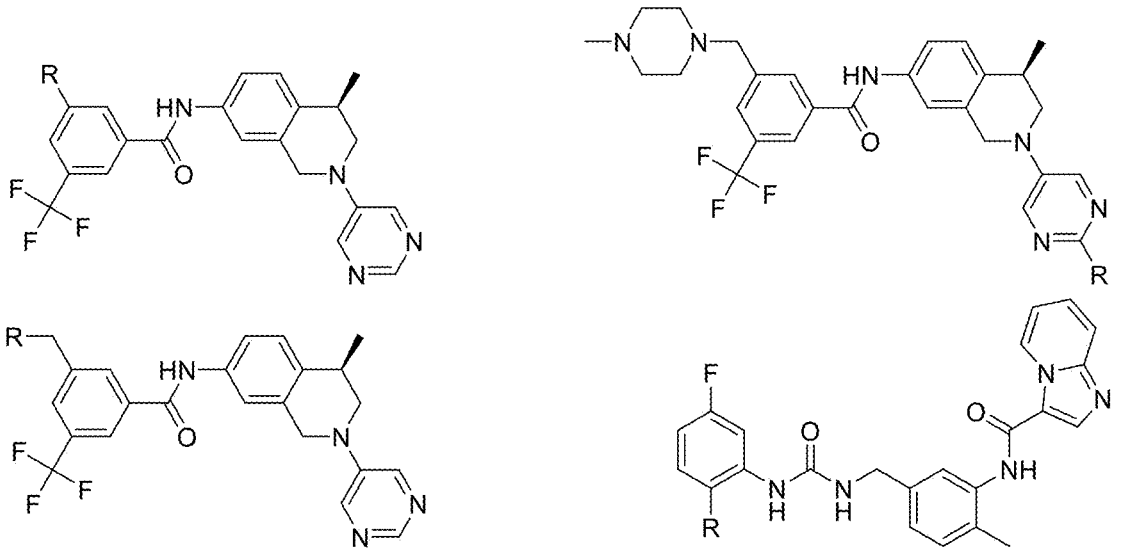


FIG. 8ZZZ

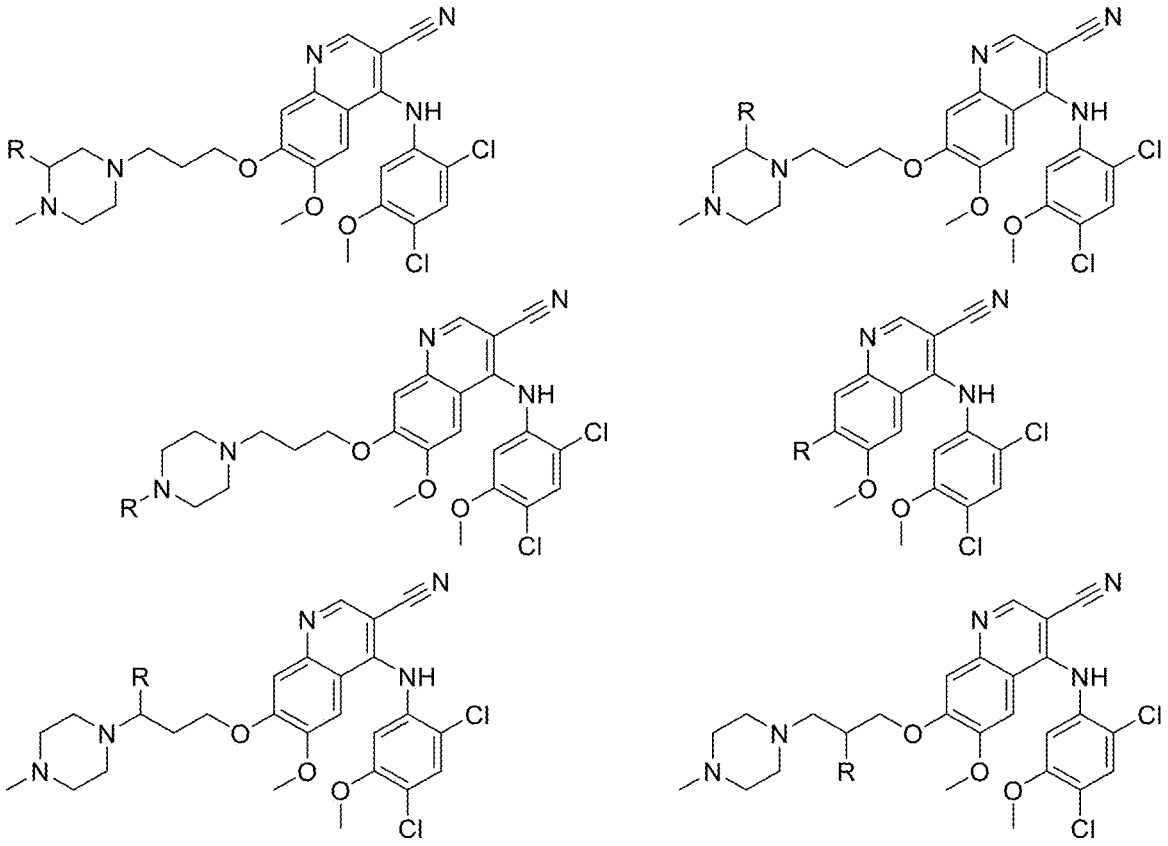


FIG. 8AAAA

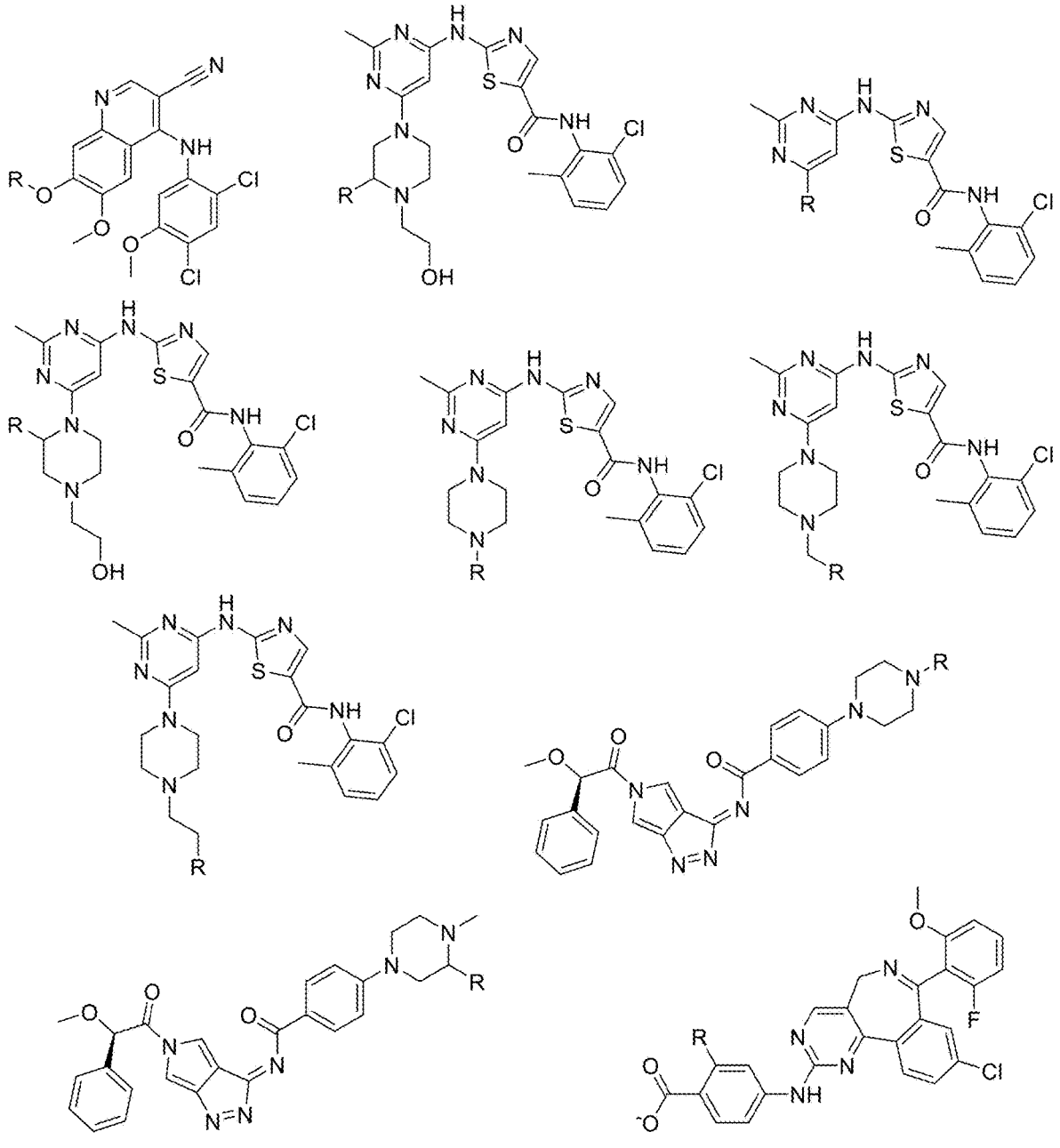


FIG. 8BBBB

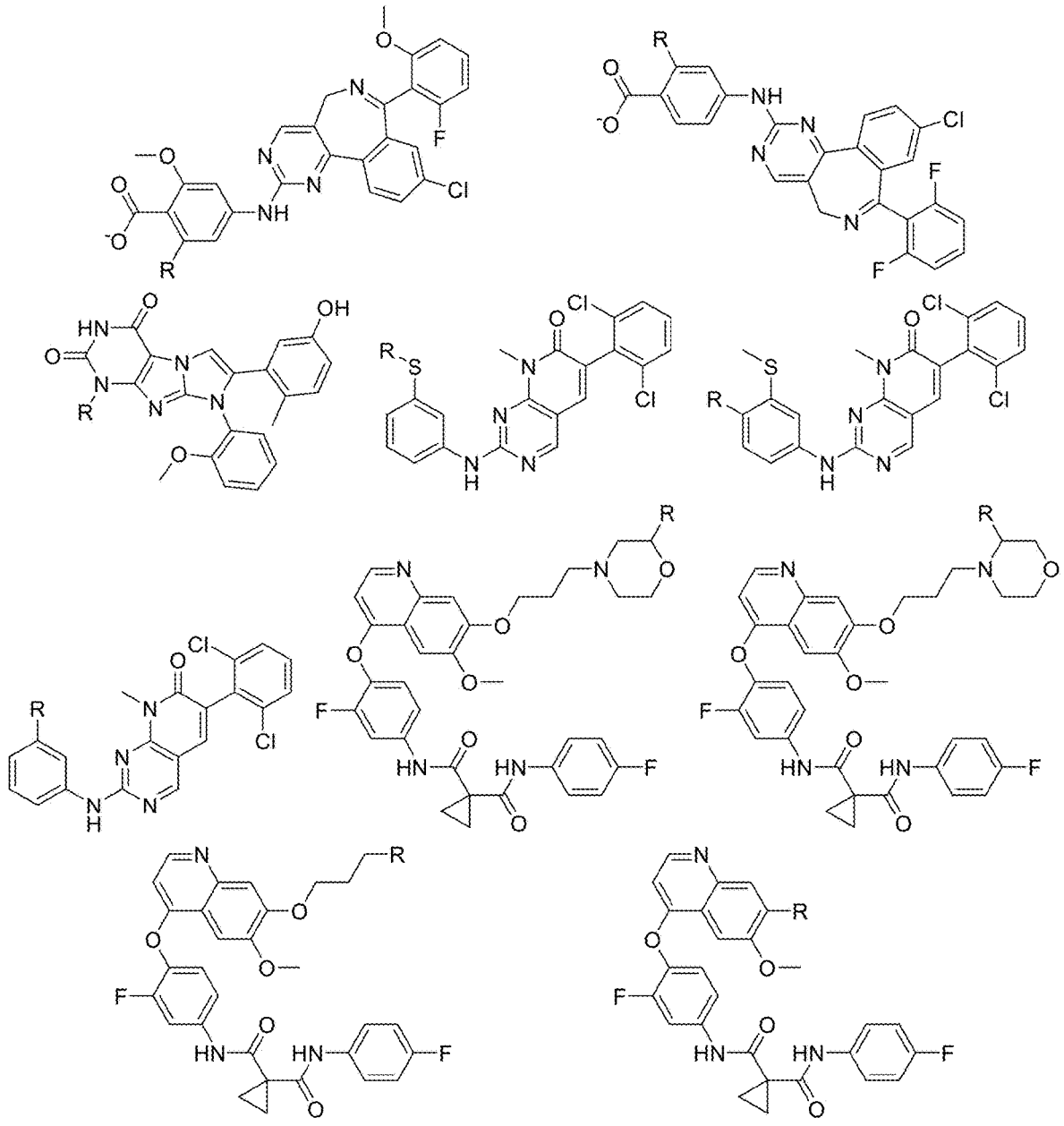


FIG. 8CCCC

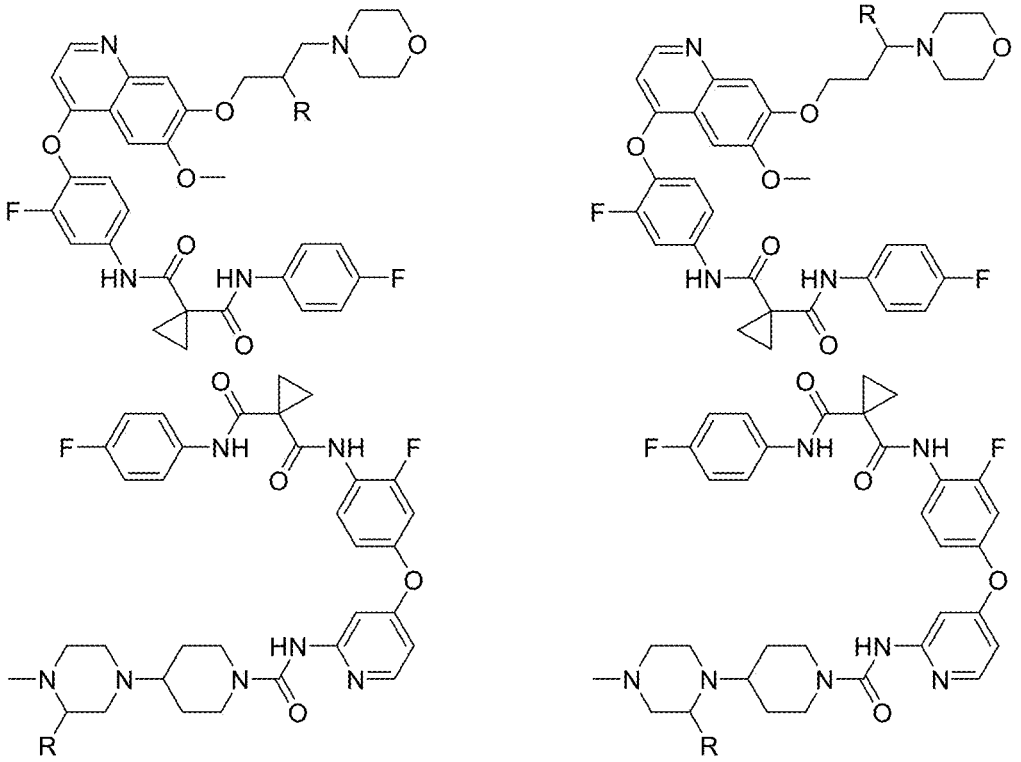


FIG. 8DDDD

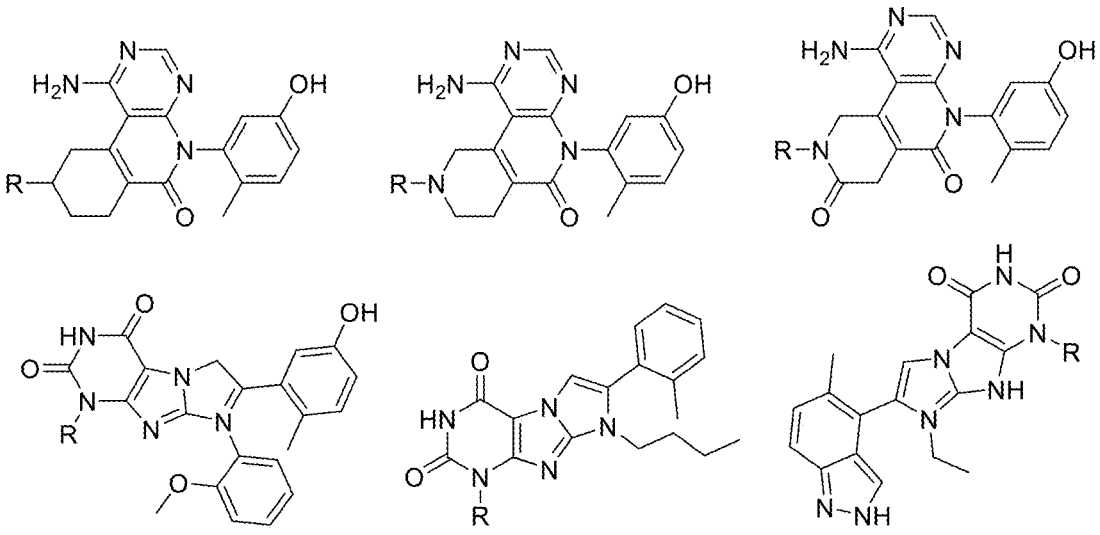


FIG. 8EEEE

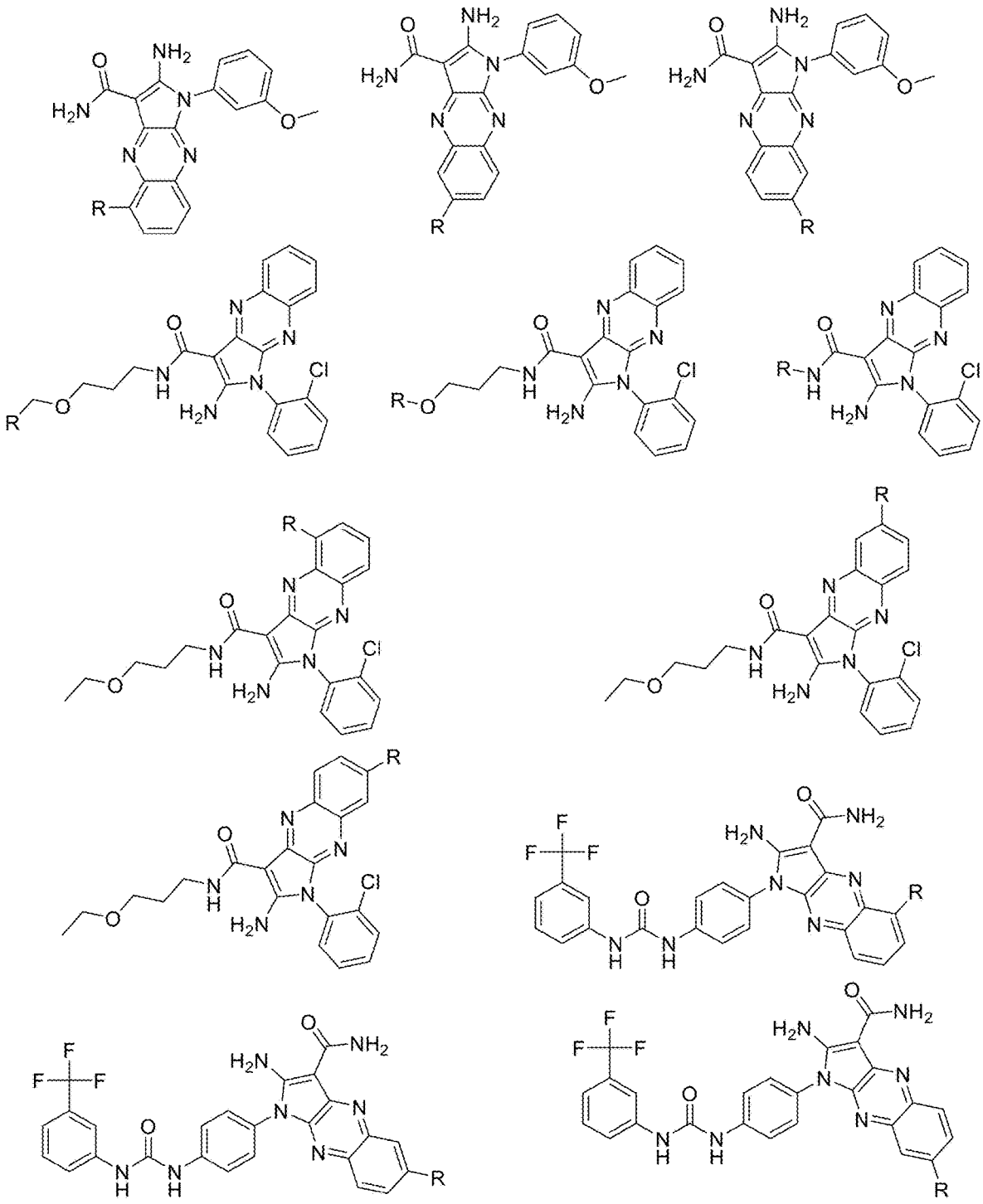


FIG. 8FFFF

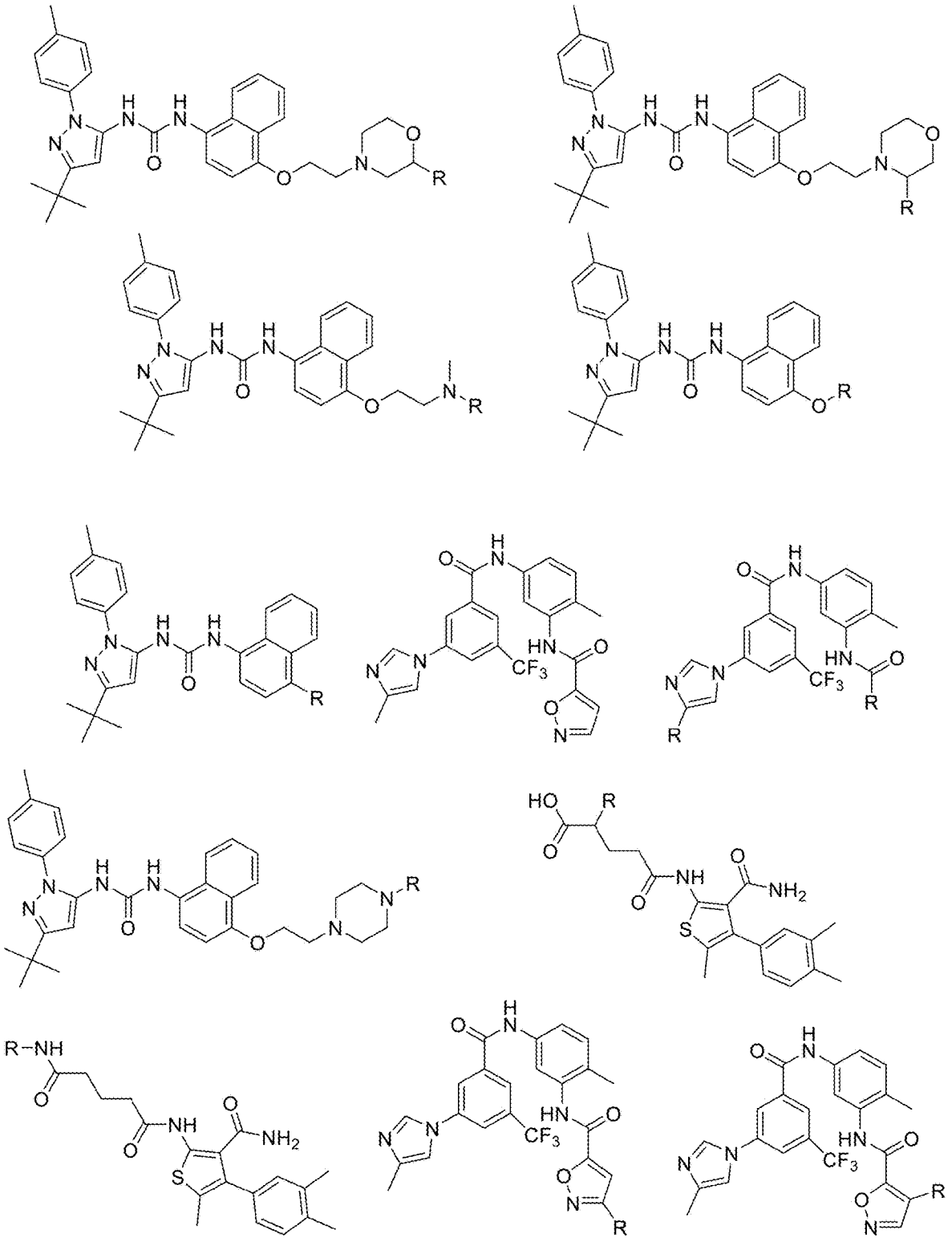


FIG. 8GGGG

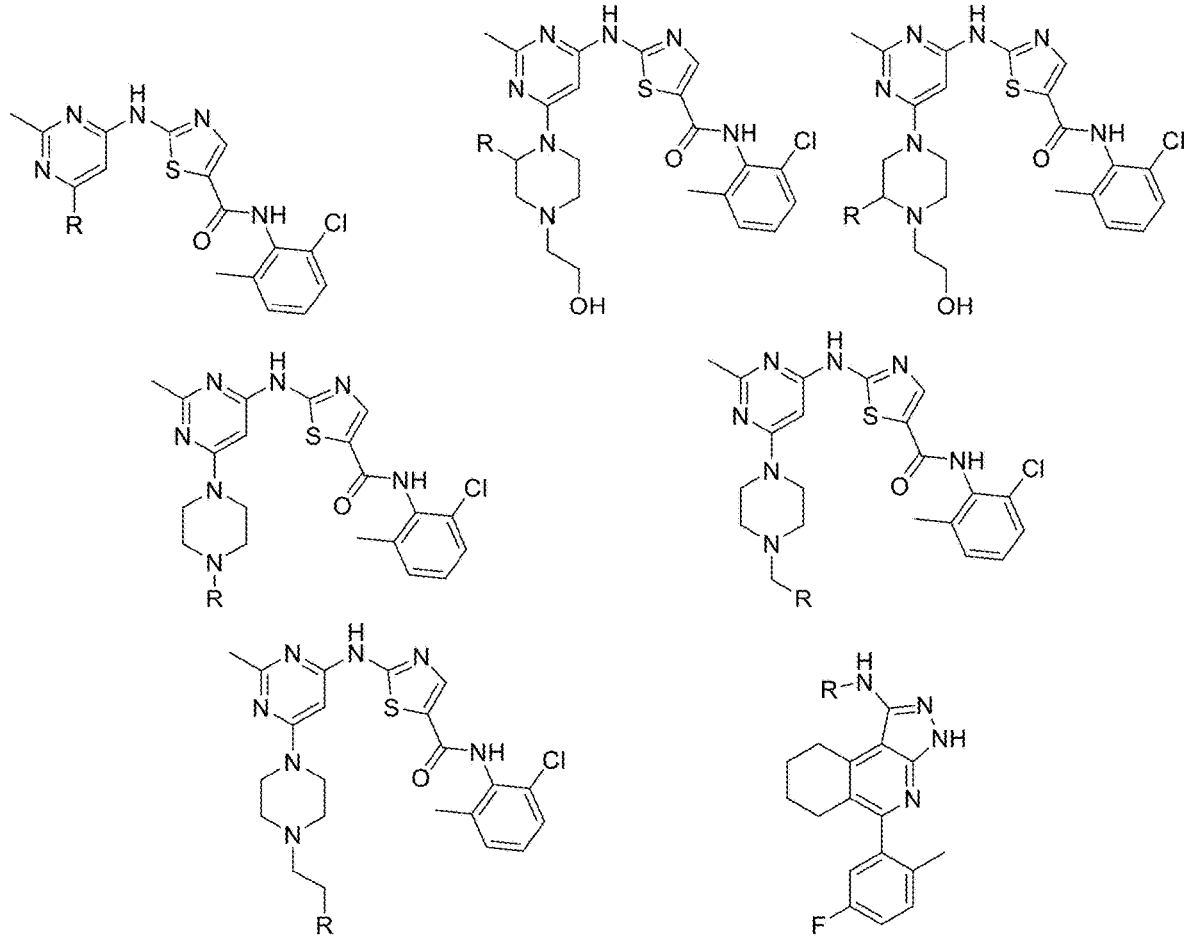


FIG. 8HHHH

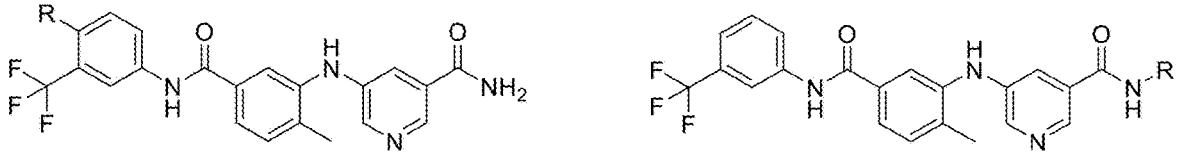


FIG. 8IIII

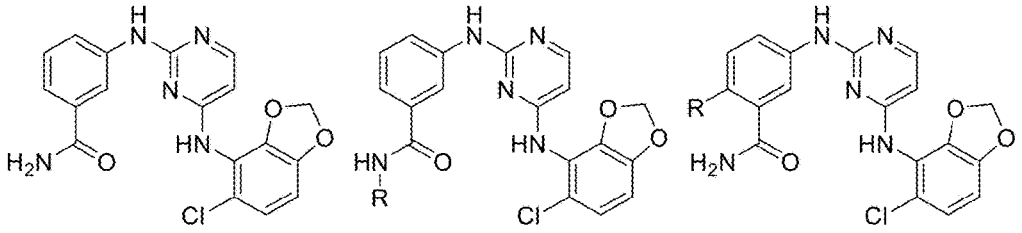


FIG. 8JJJ

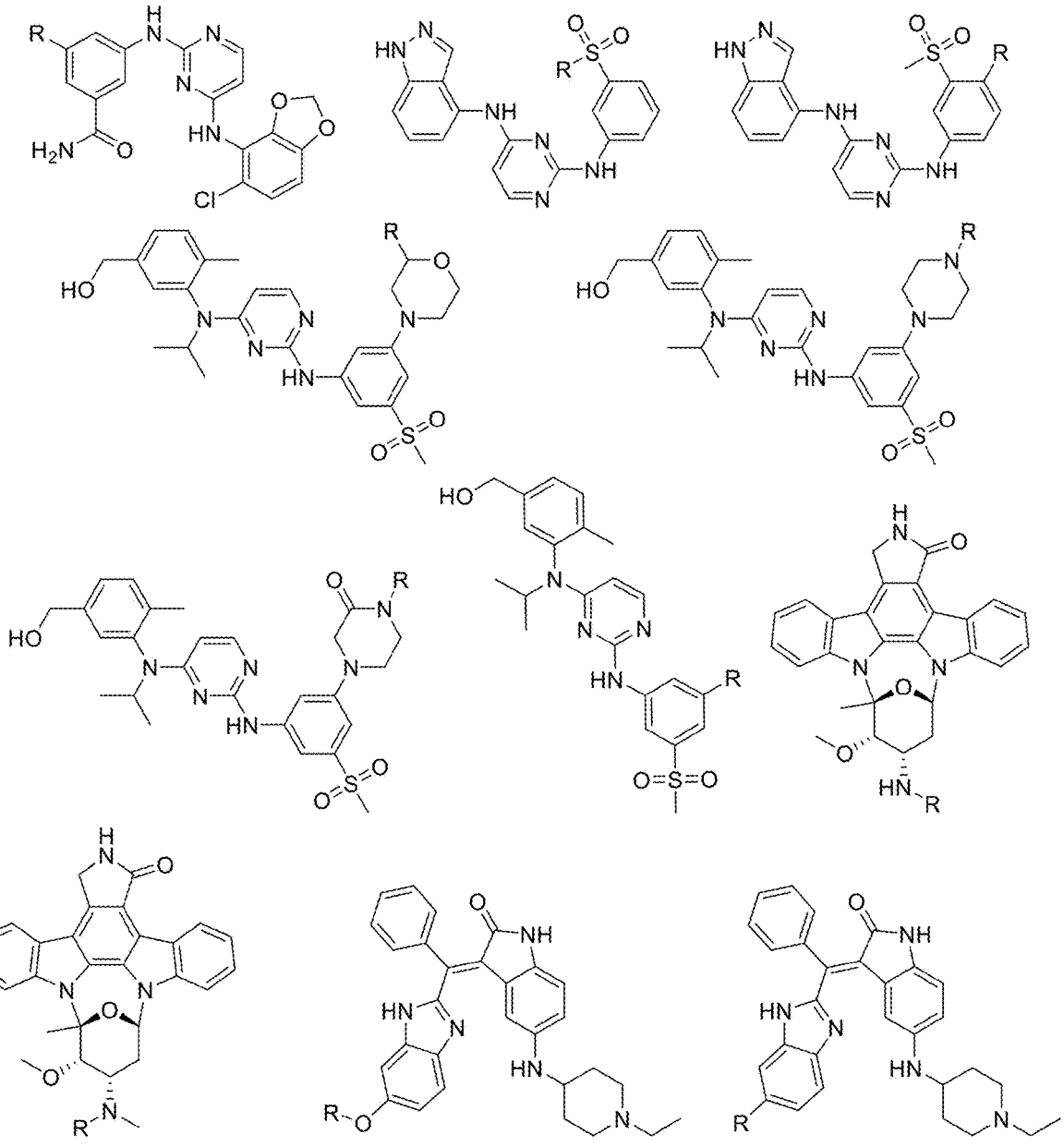


FIG. 8KKKK

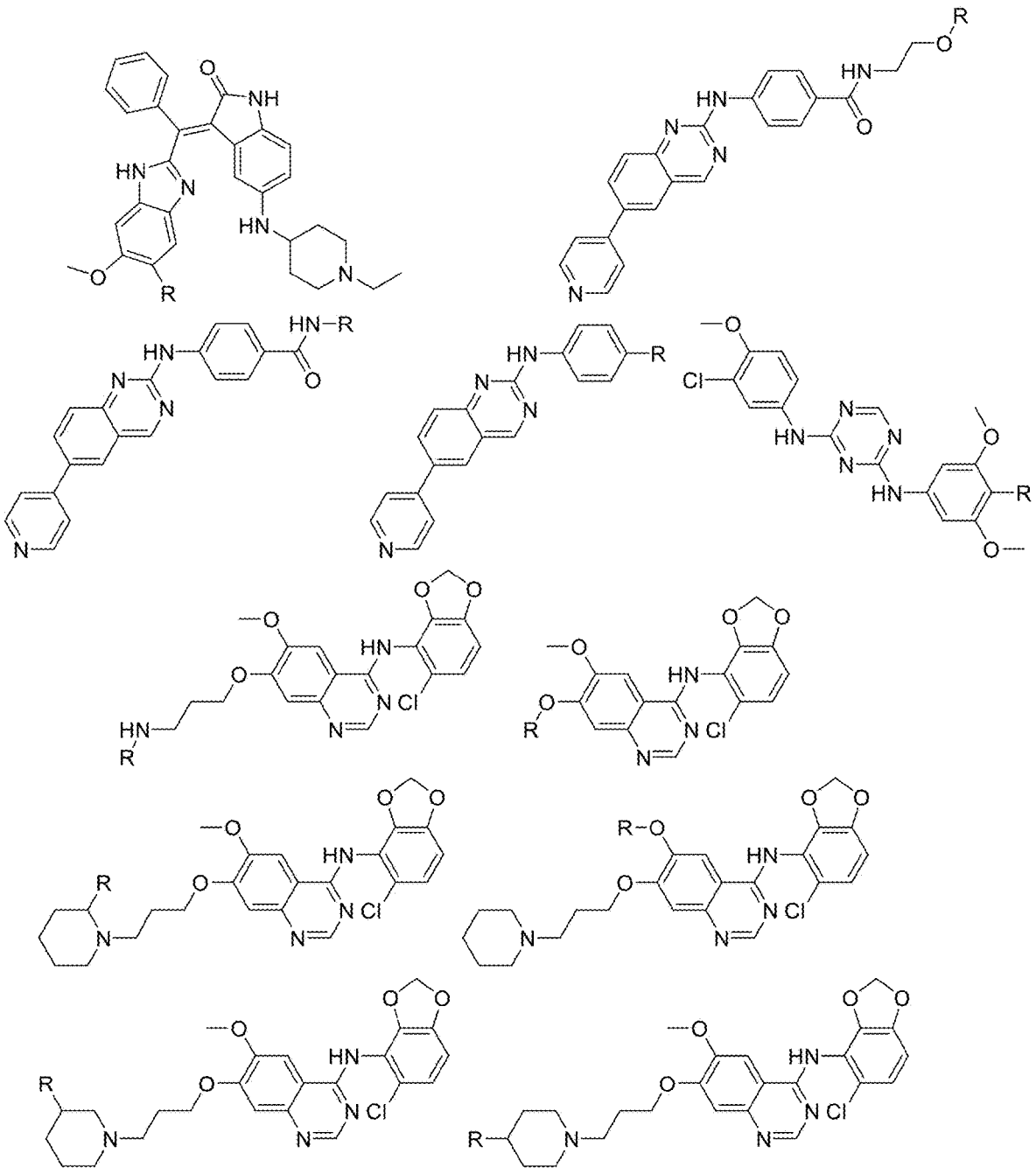


FIG. 8LLLL

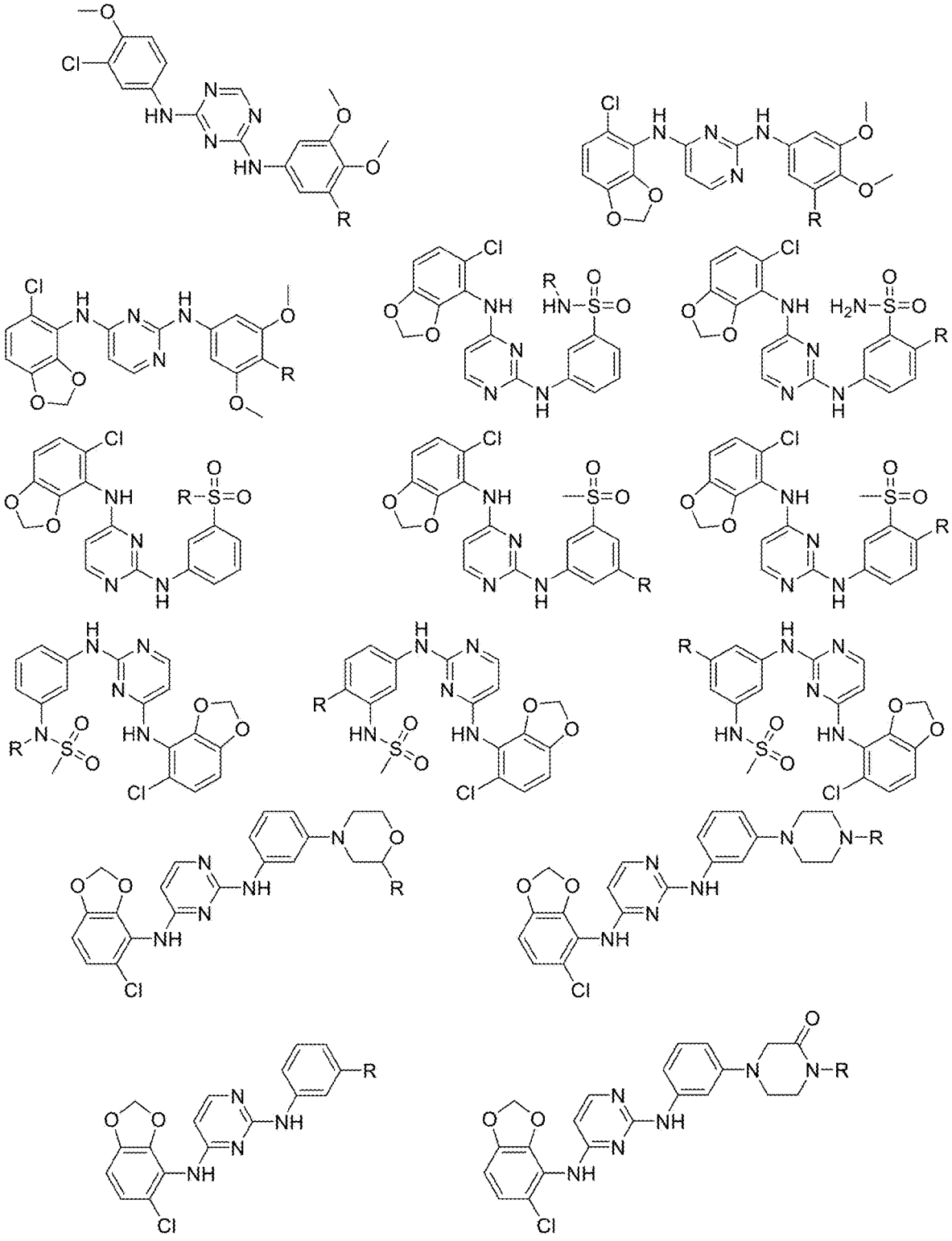


FIG. 8MMMM

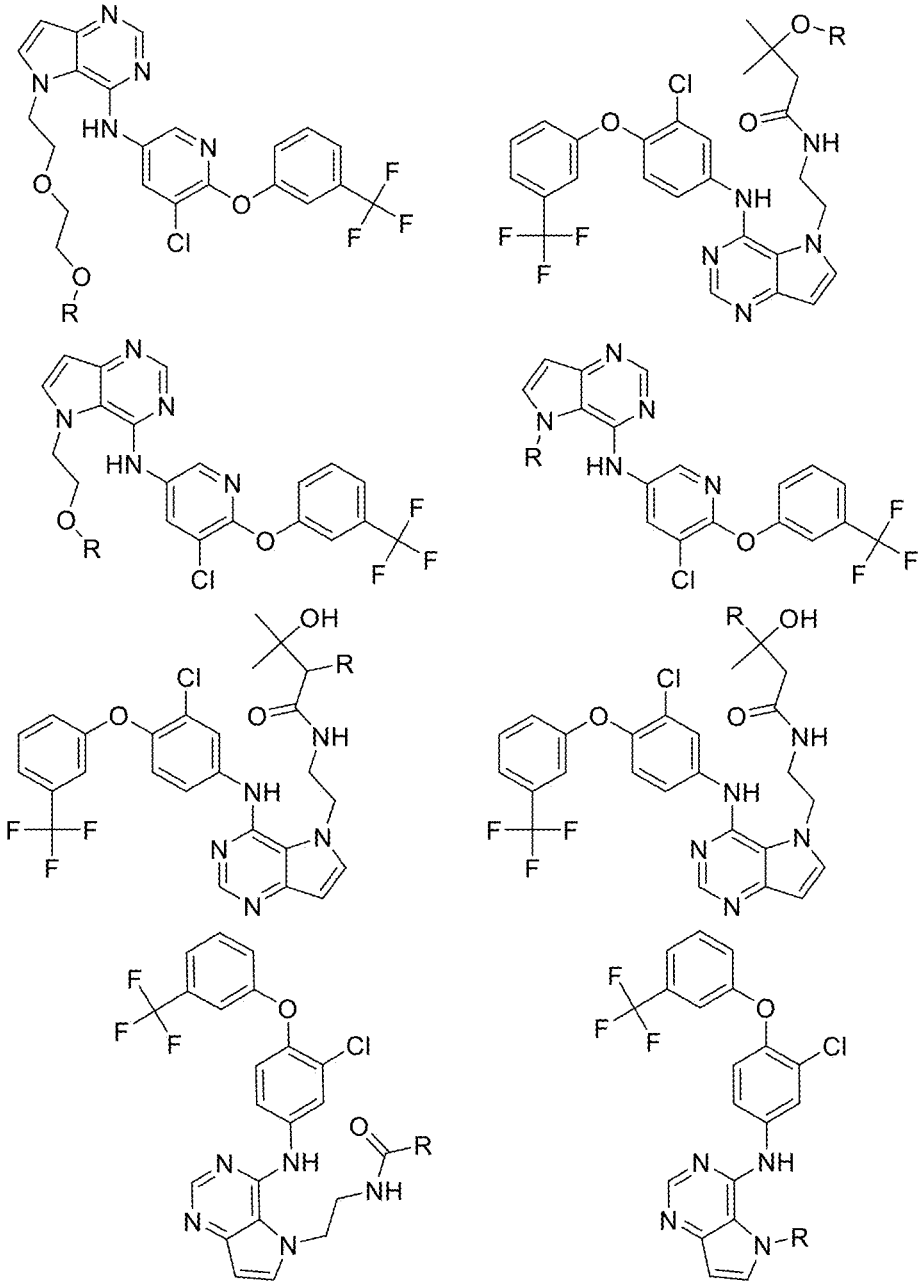


FIG. 8NNNN

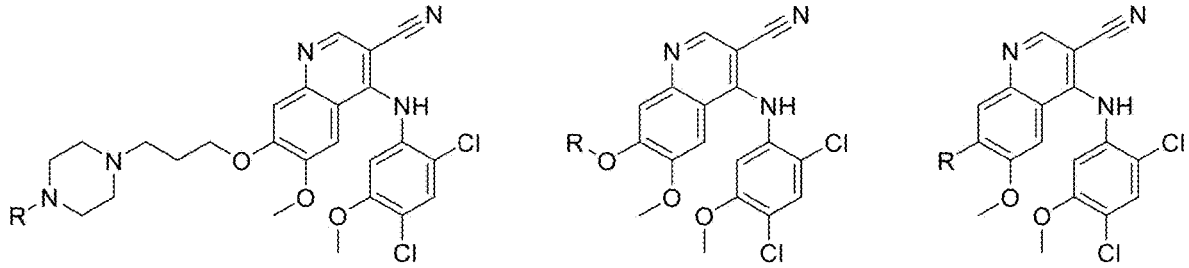


FIG. 8OOOO

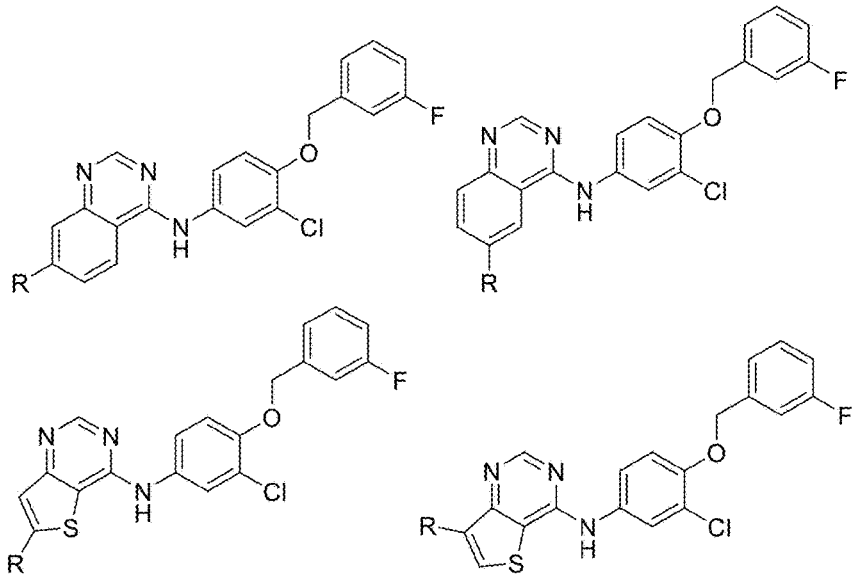


FIG. 8PPPP

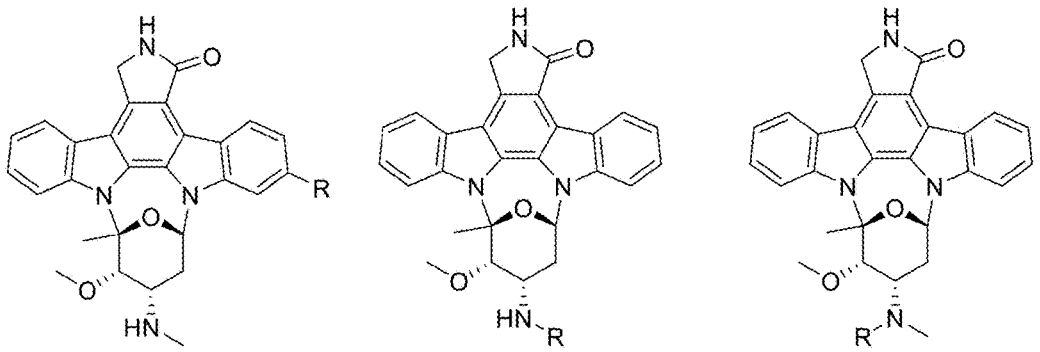


FIG. 8QQQQ

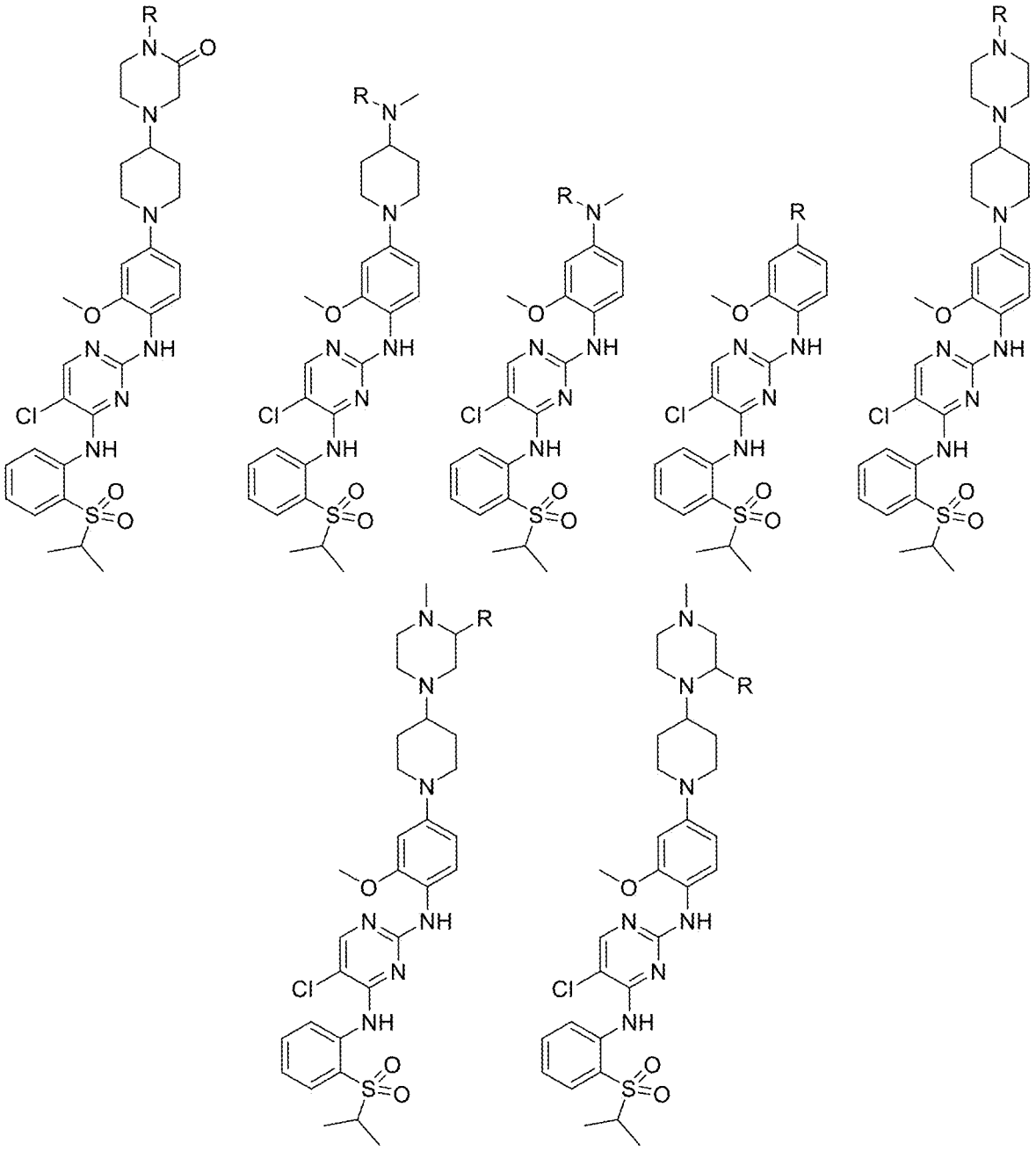


FIG. 8RRRR

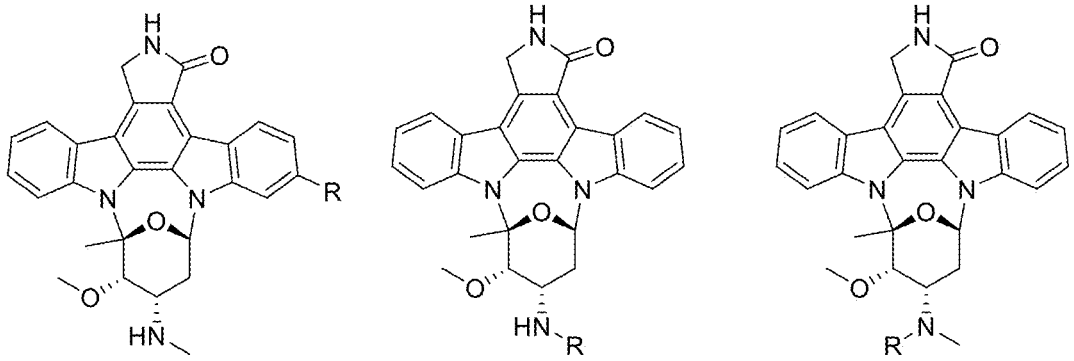


FIG. 8SSSS

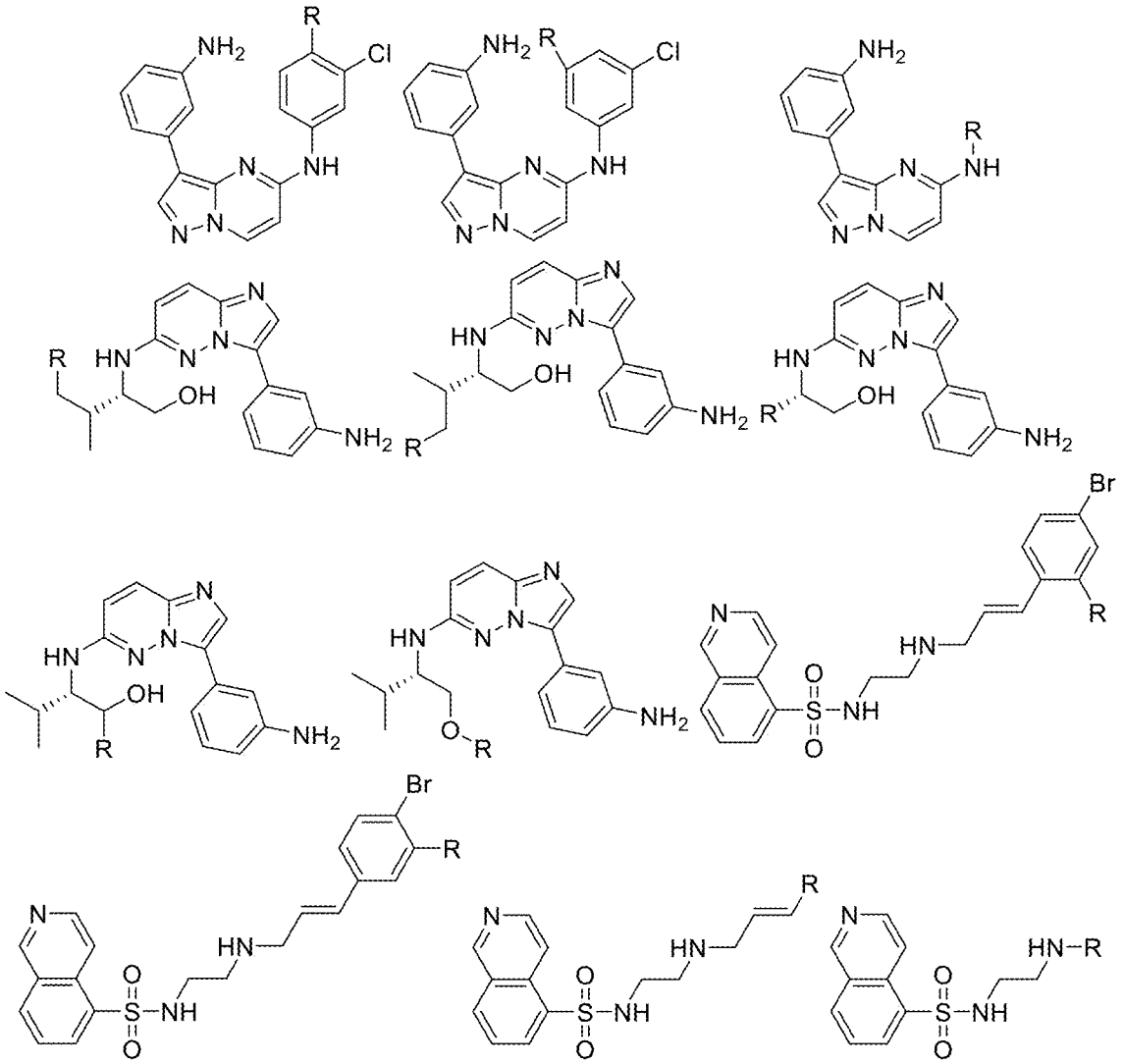


FIG. 8TTTT

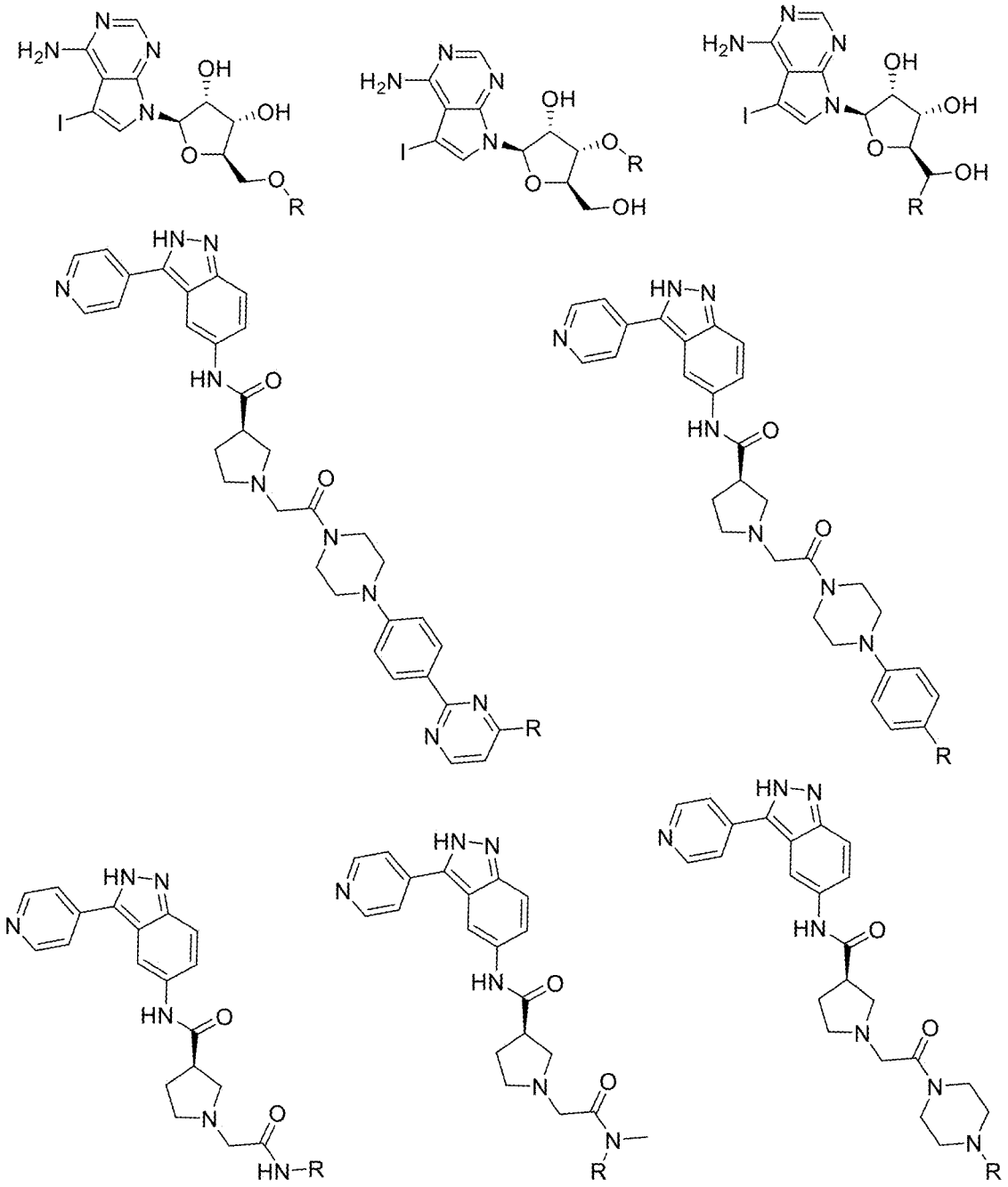


FIG. 8UUUU

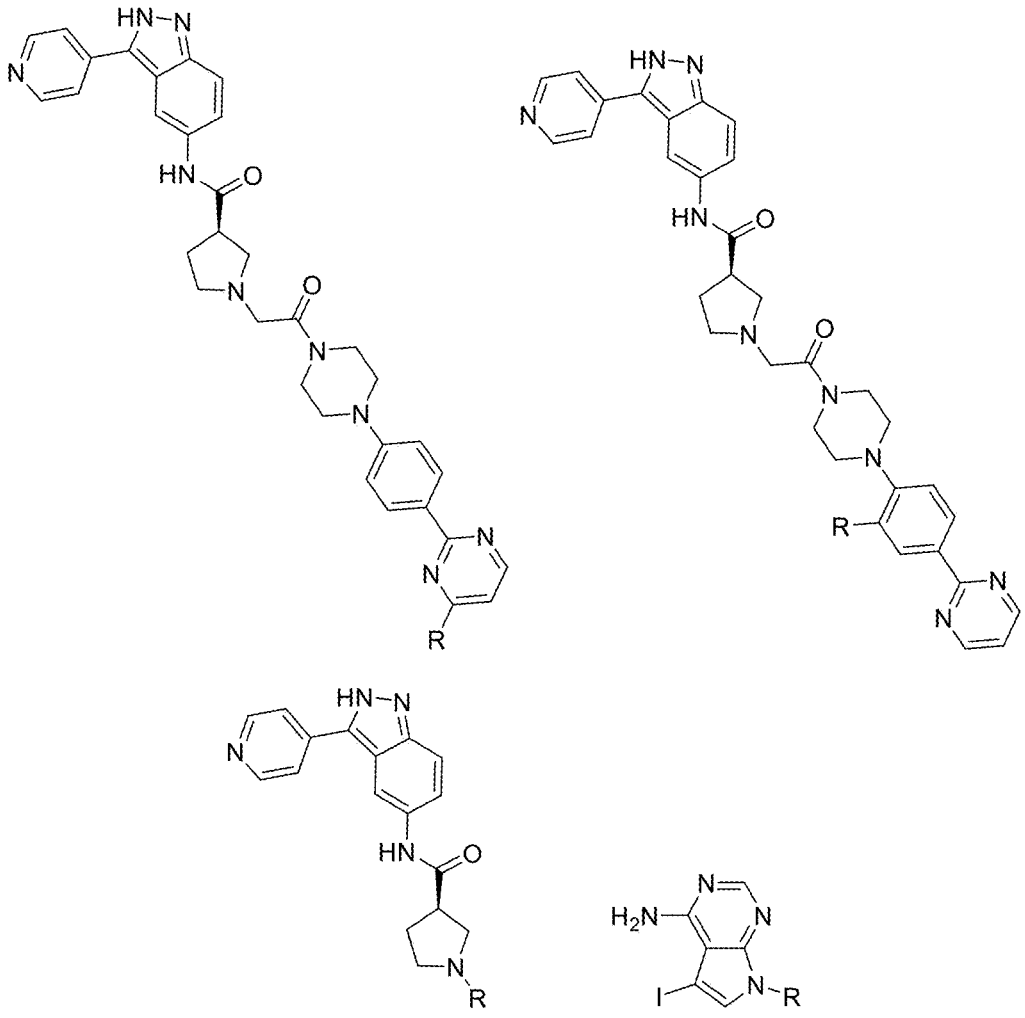


FIG. 8VVVV

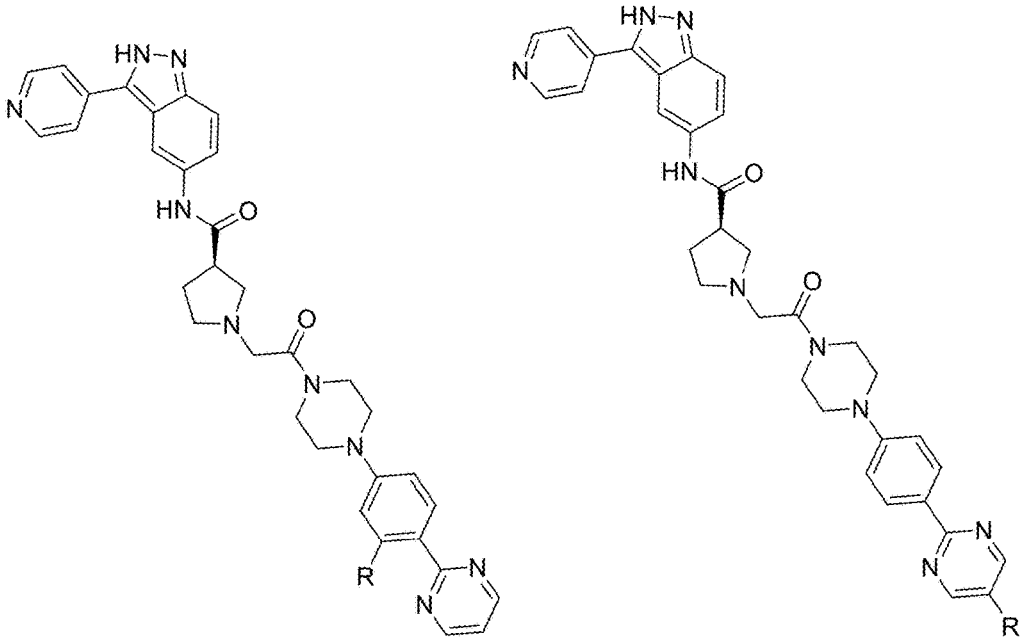


FIG. 8WWWW

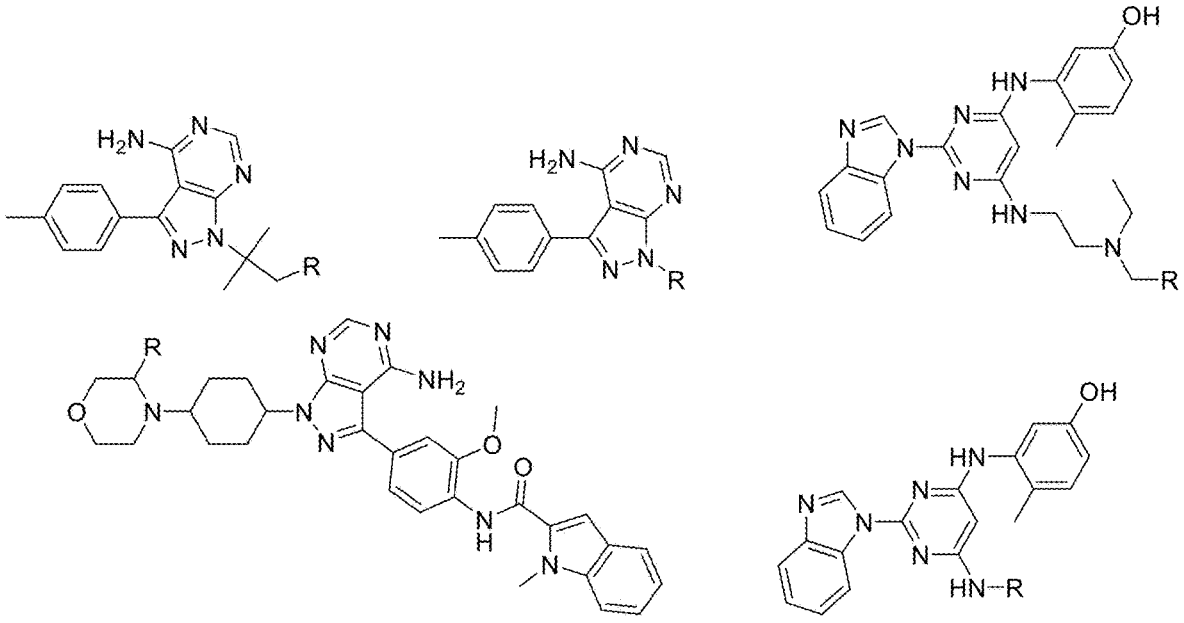


FIG. 8XXXX

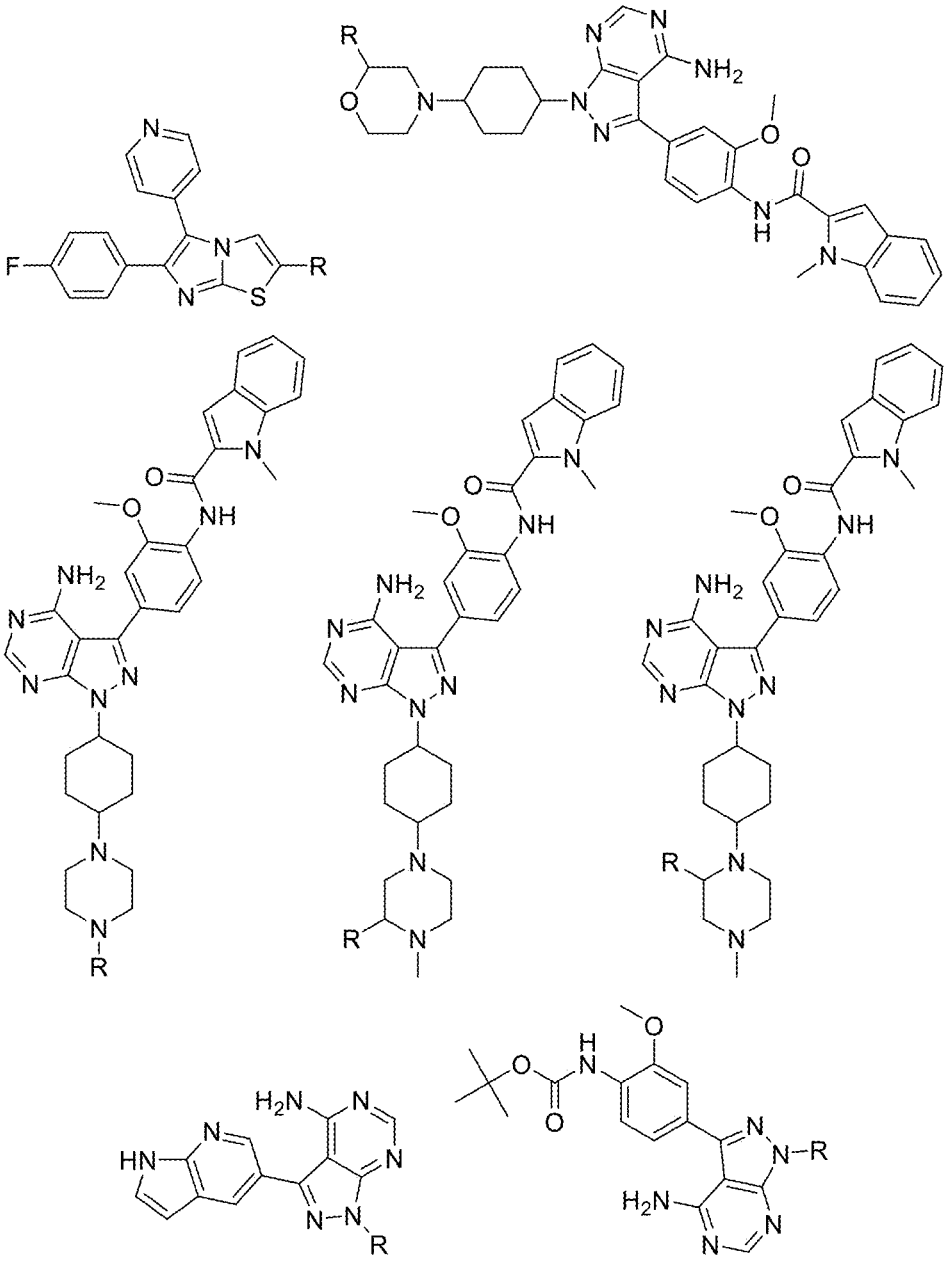


FIG. 8YYYY

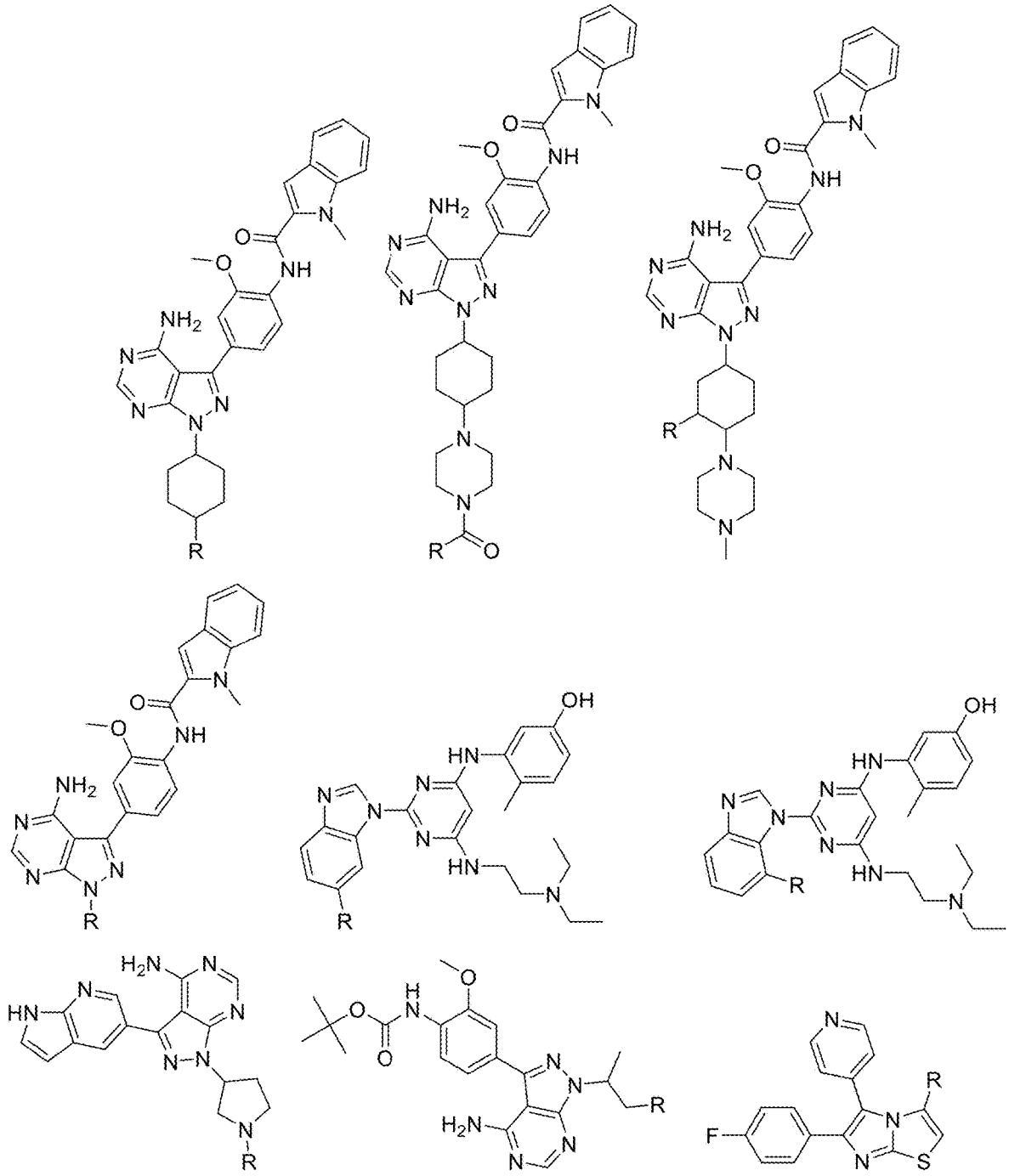


FIG. 8ZZZZ

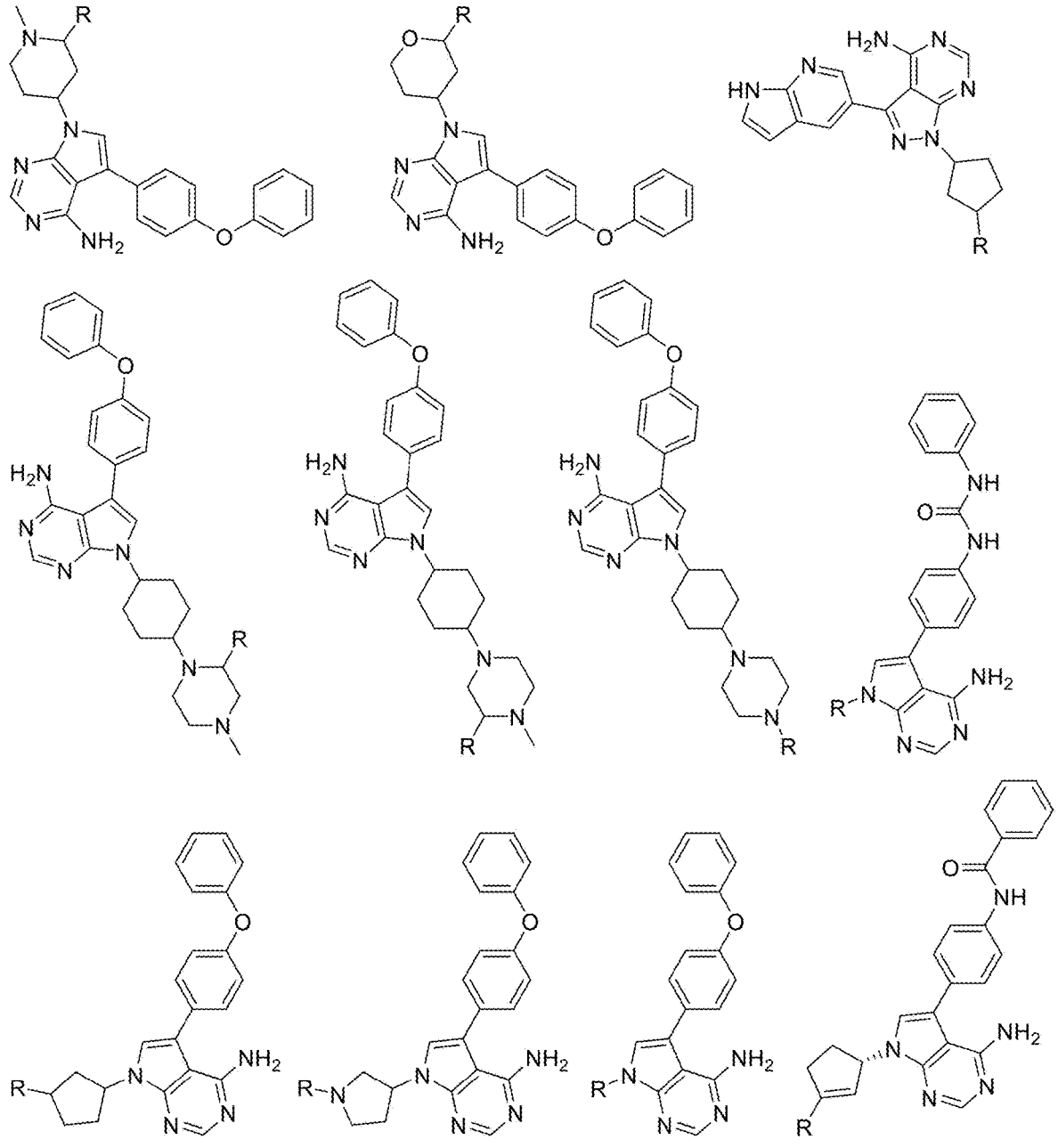


FIG. 8AAAAA

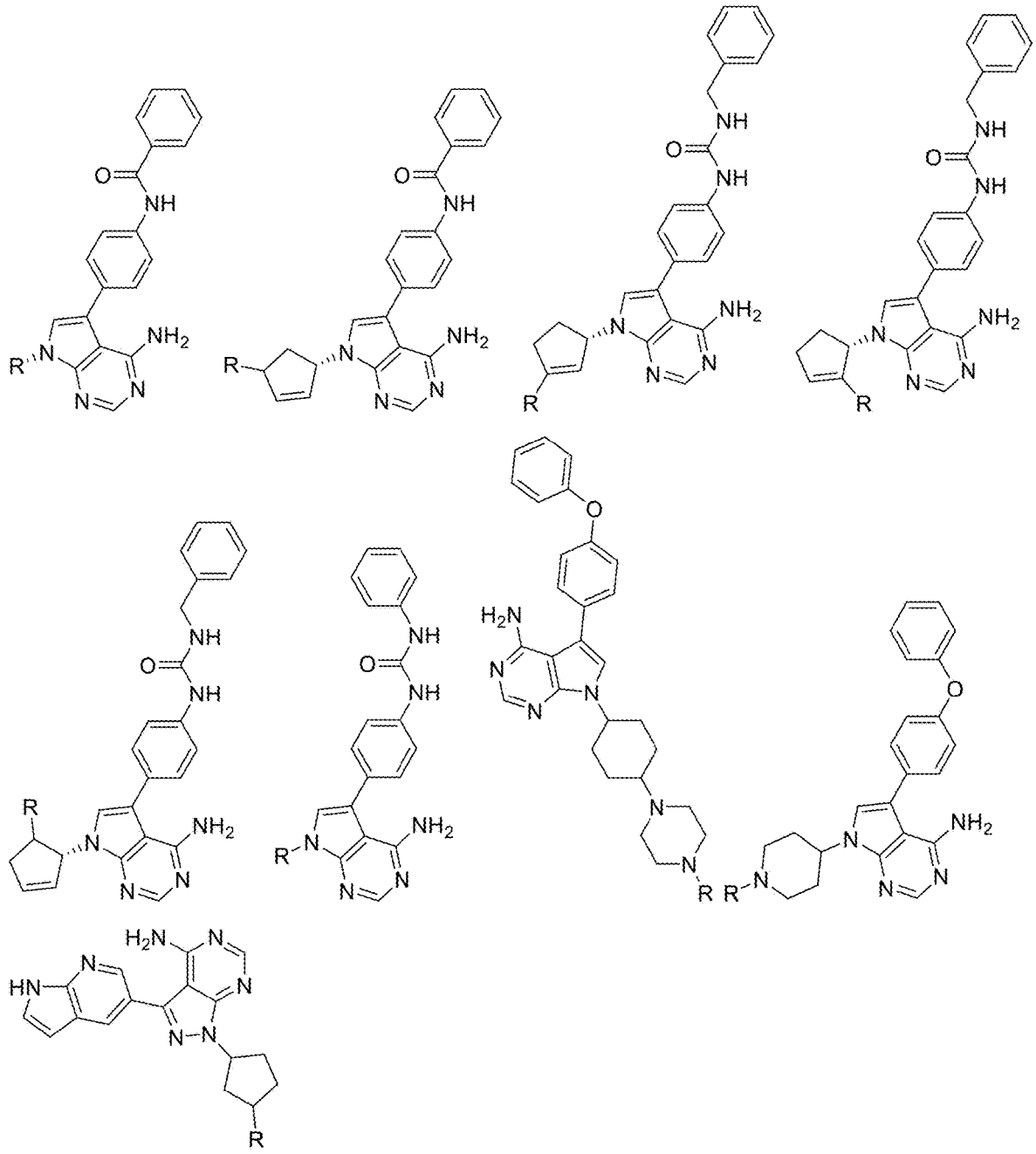


FIG. 8BBBBB

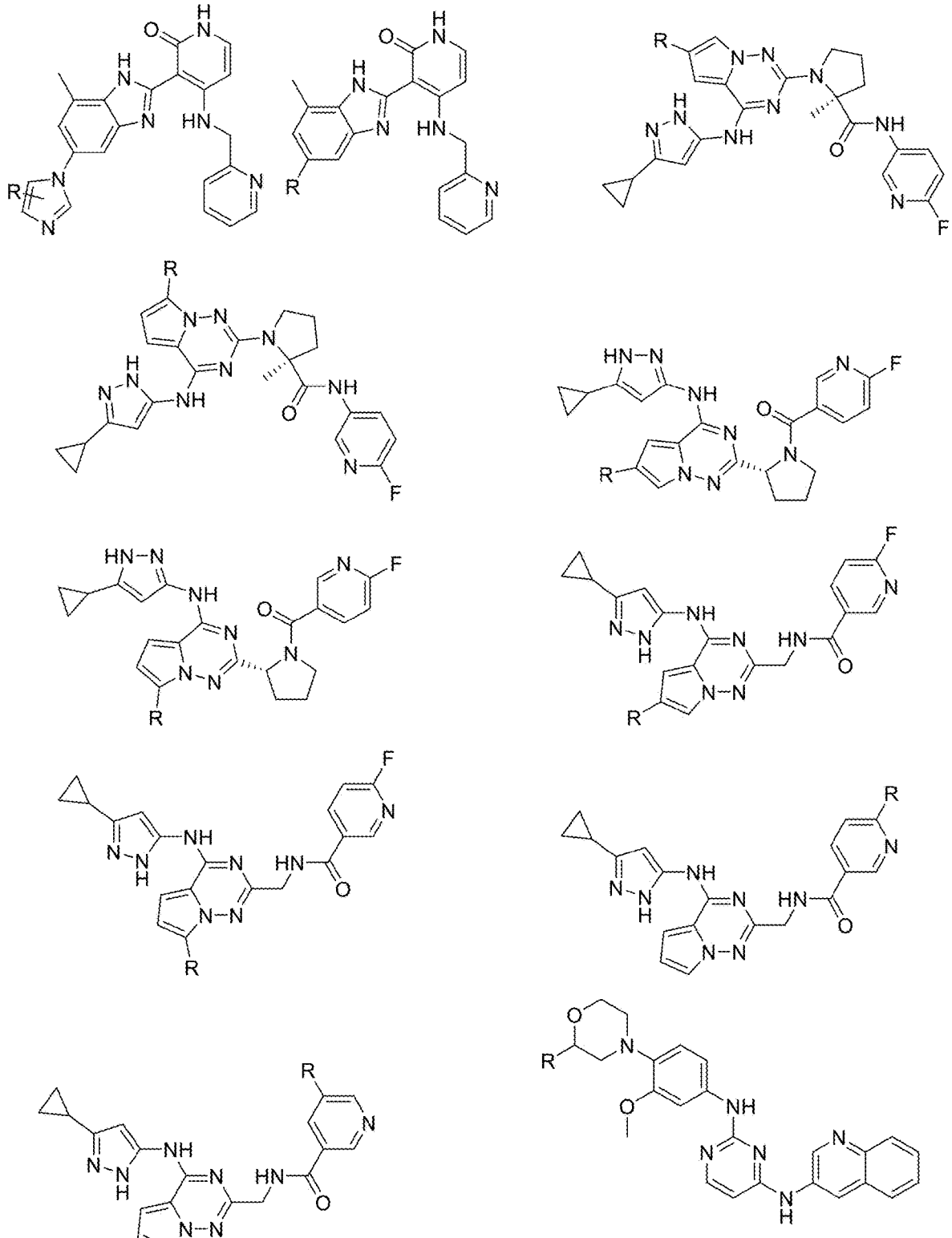


FIG. 8CCCCC

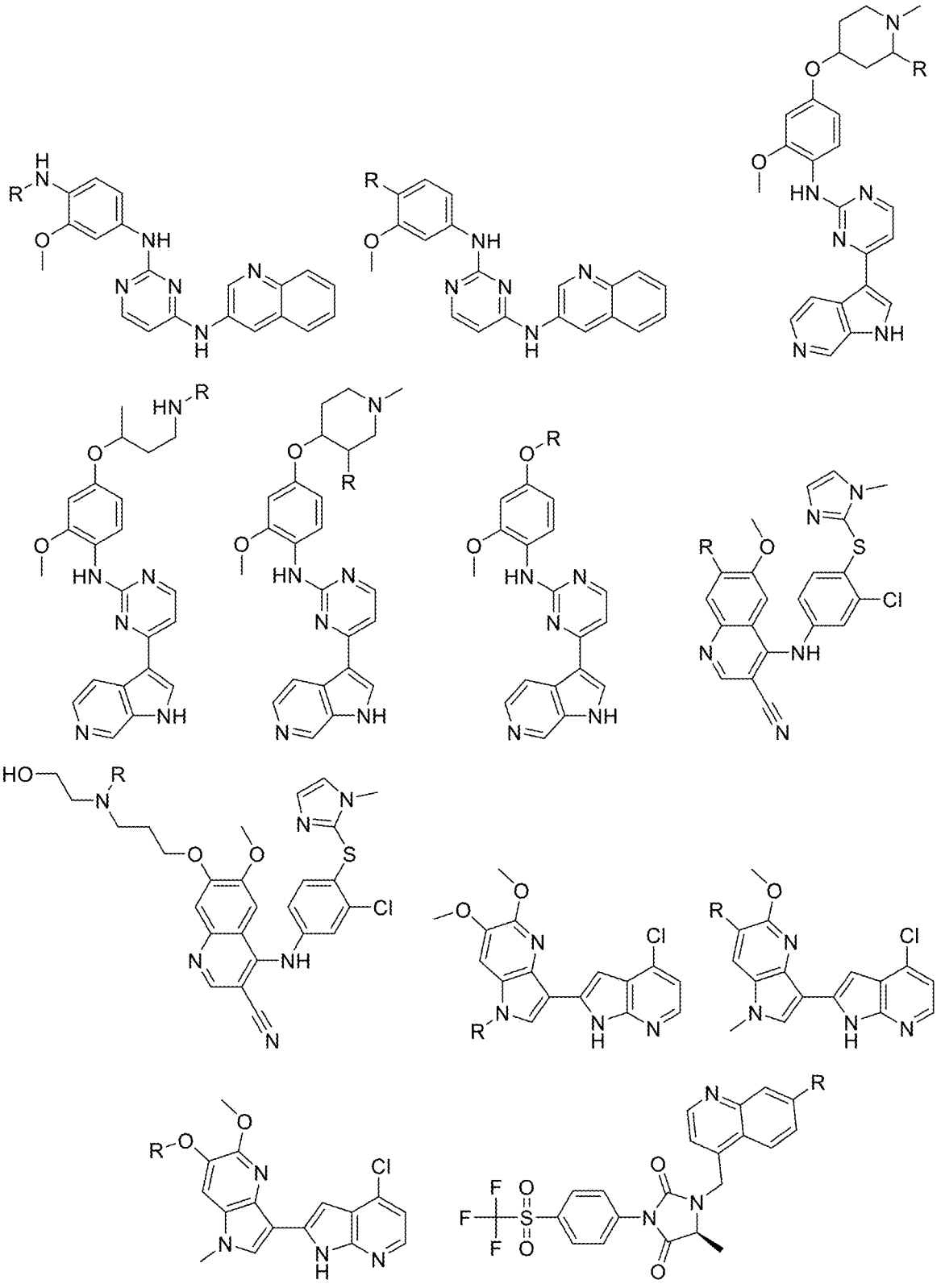


FIG. 8DDDDD

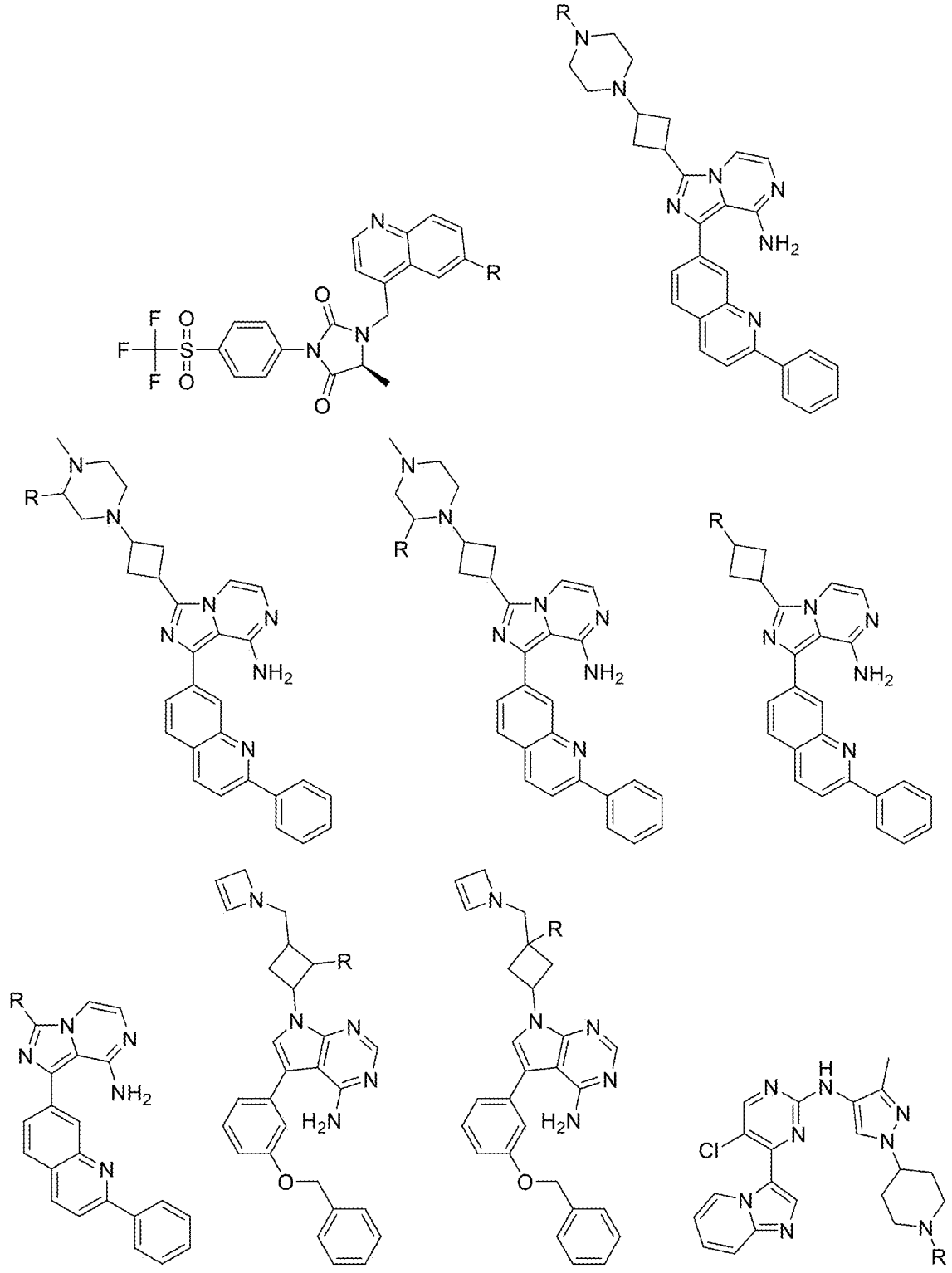


FIG. 8EEEEE

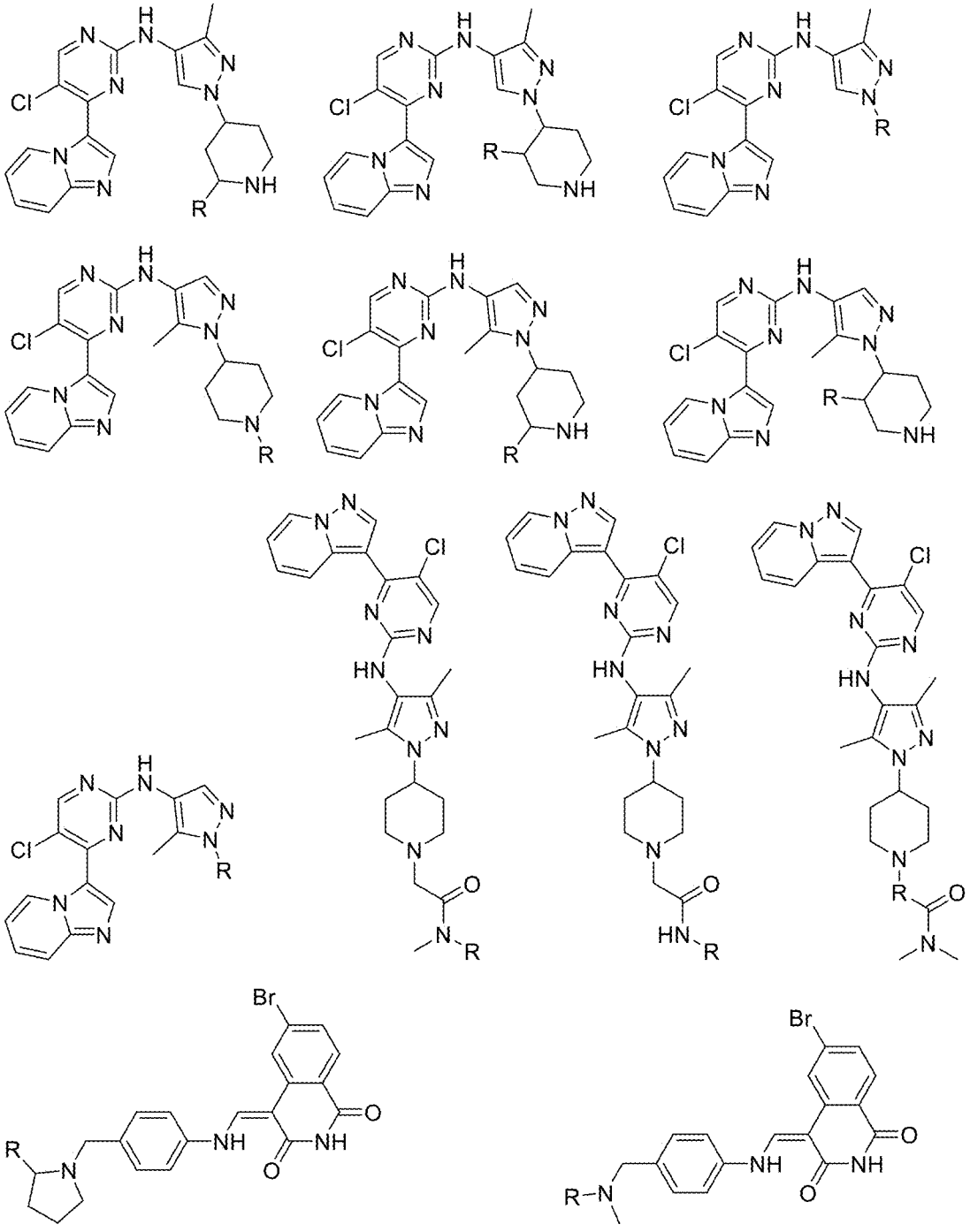


FIG. 8FFFFF

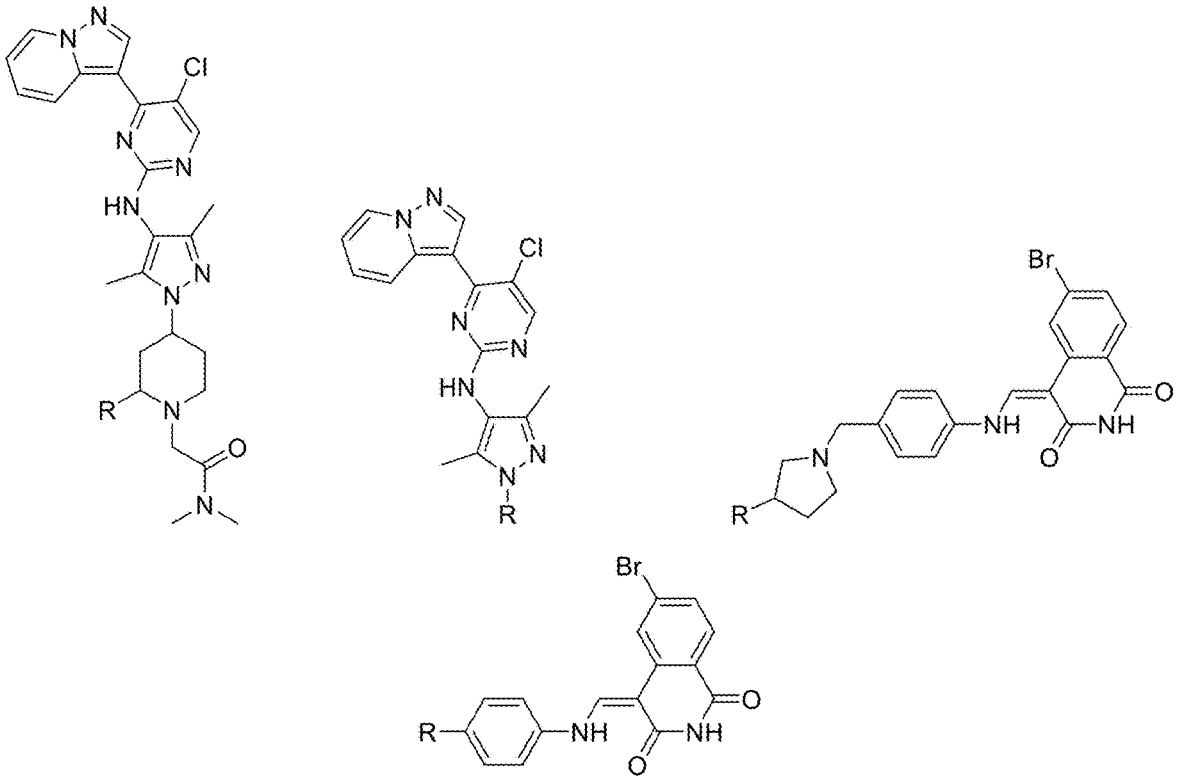


FIG. 8GGGGG

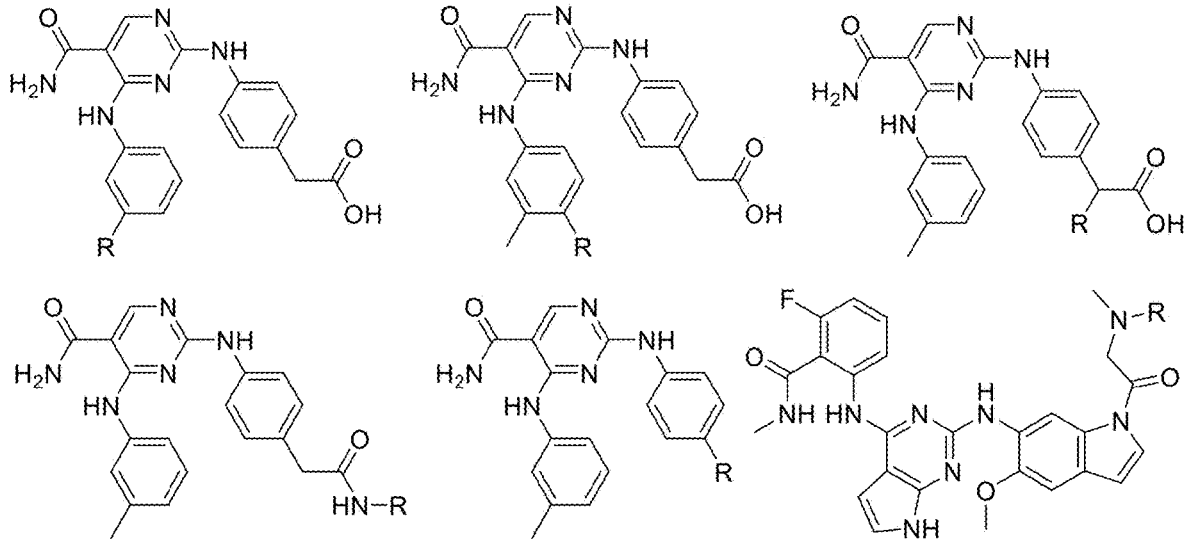


FIG. 8HHHHH

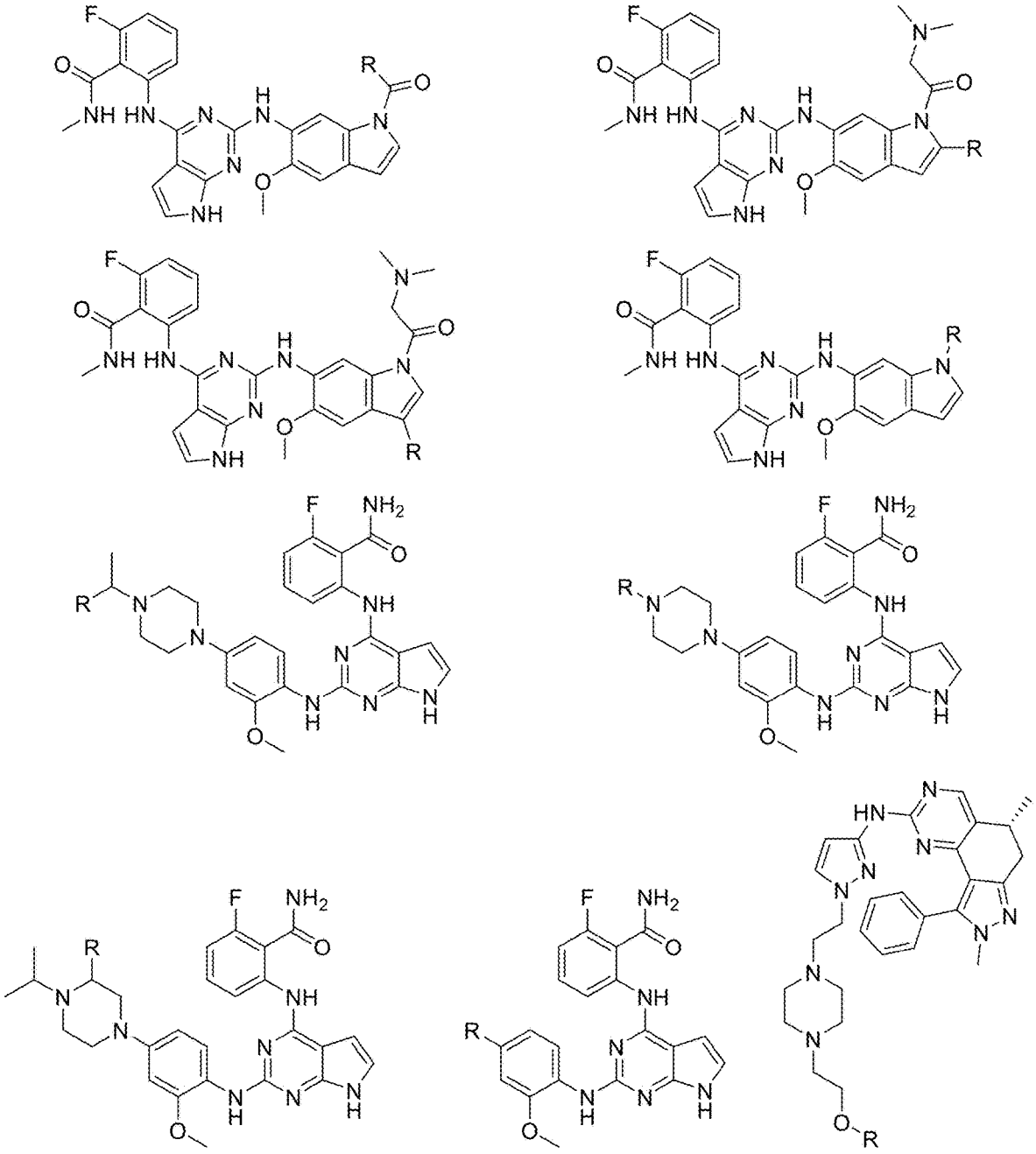


FIG. 8IIIII

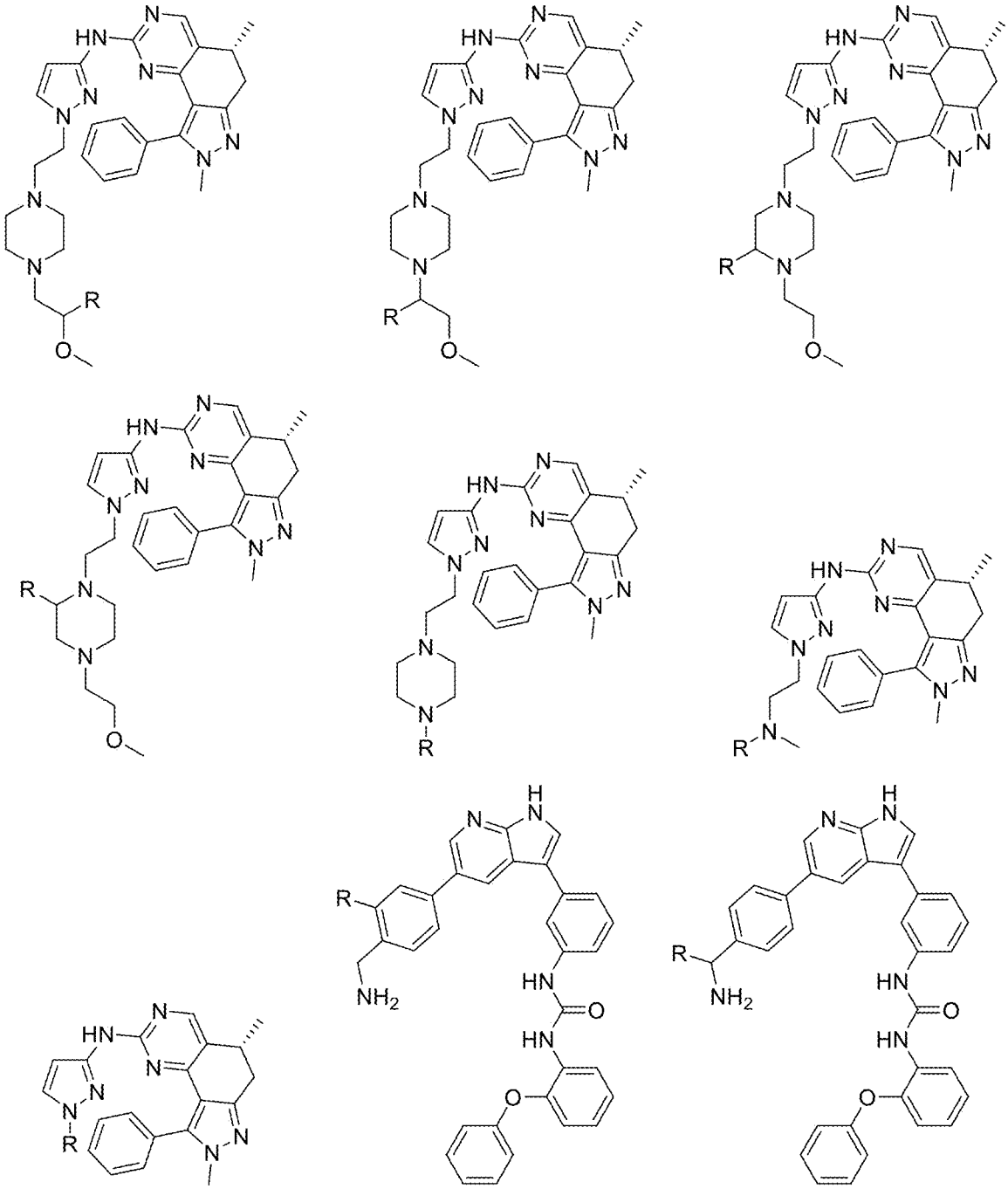


FIG. 8JJJJJ

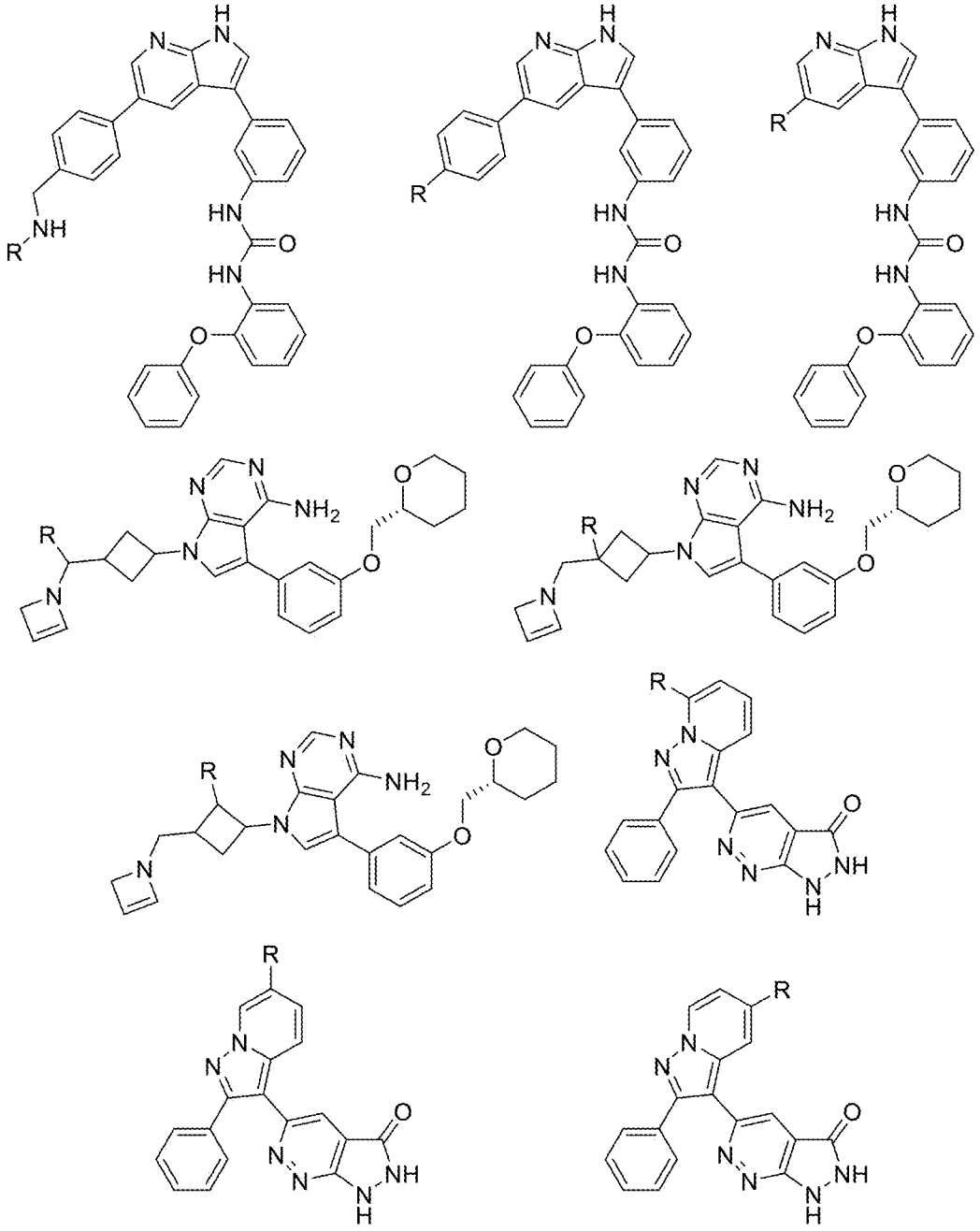


FIG. 8KKKKK

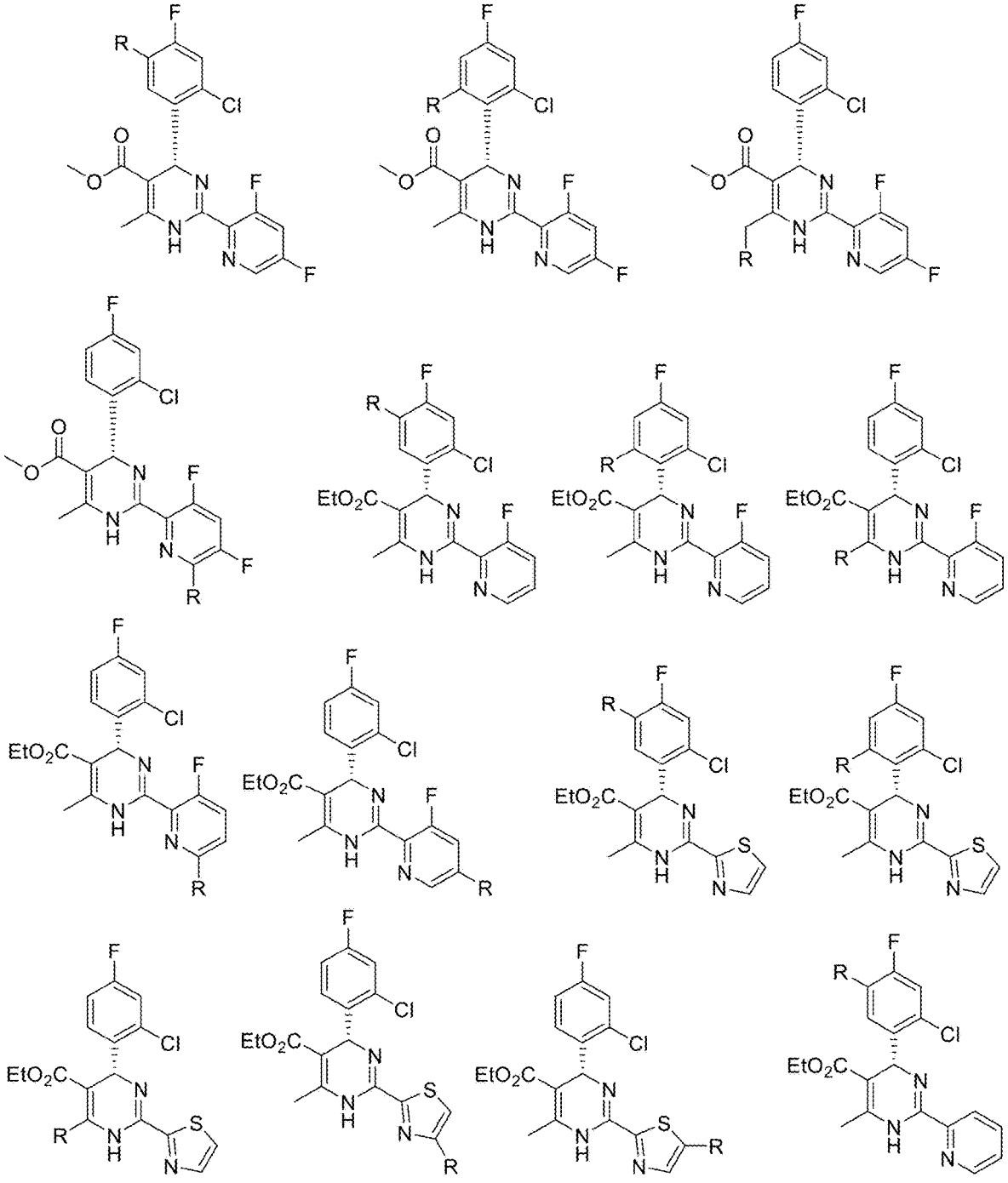


FIG. 8LLLLL

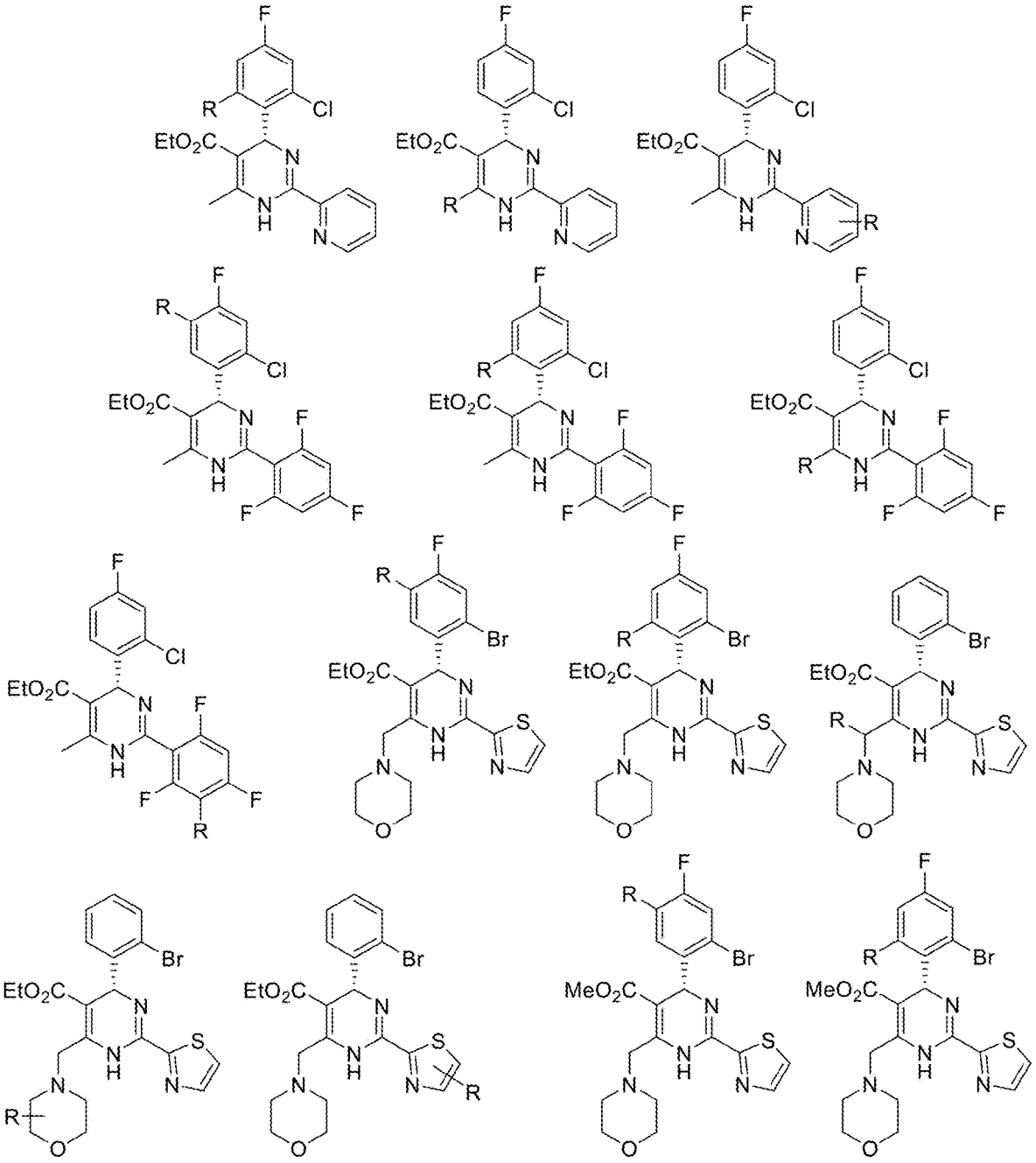


FIG. 8MMMMM

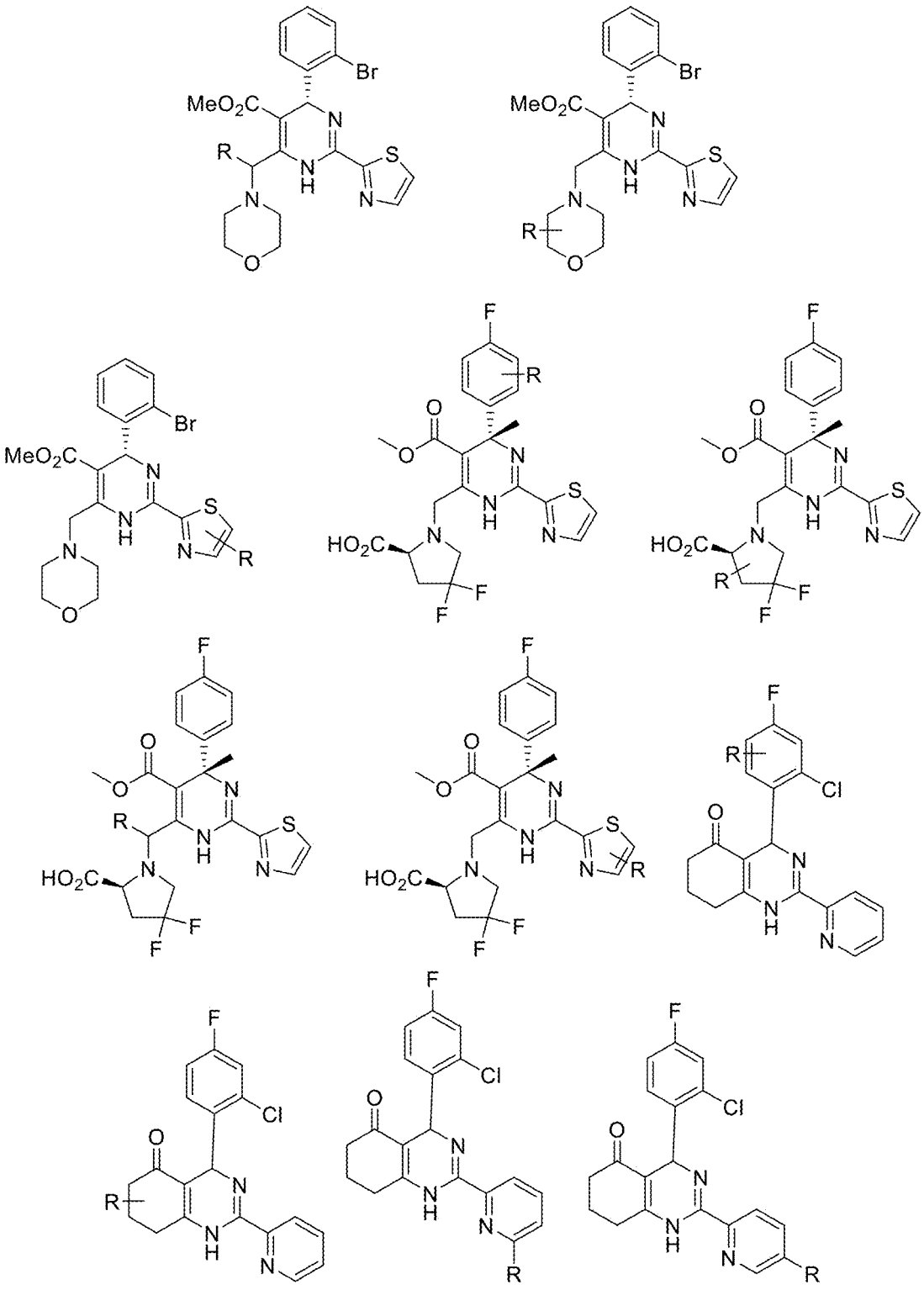


FIG. 8NNNNN

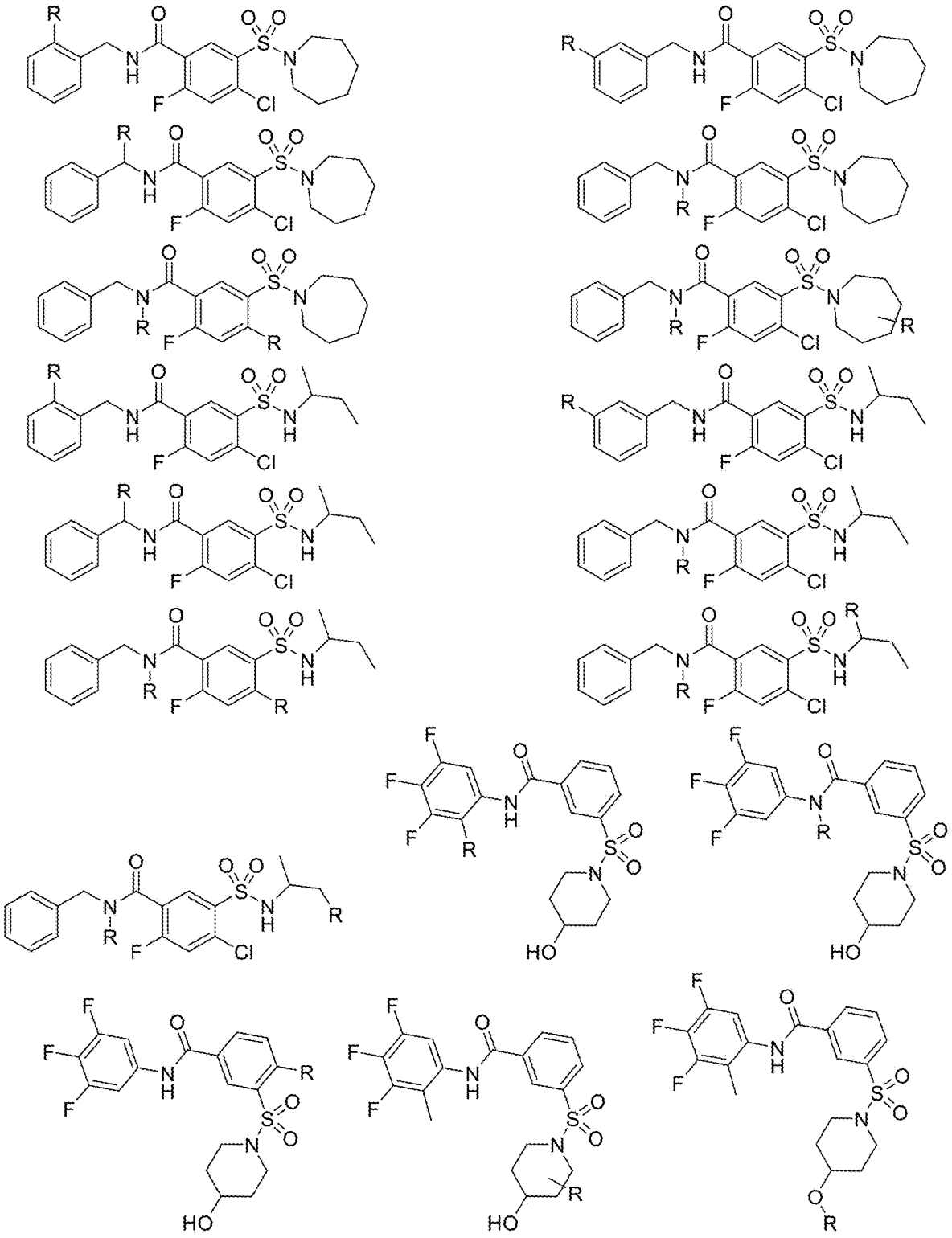


FIG. 8OOOOO

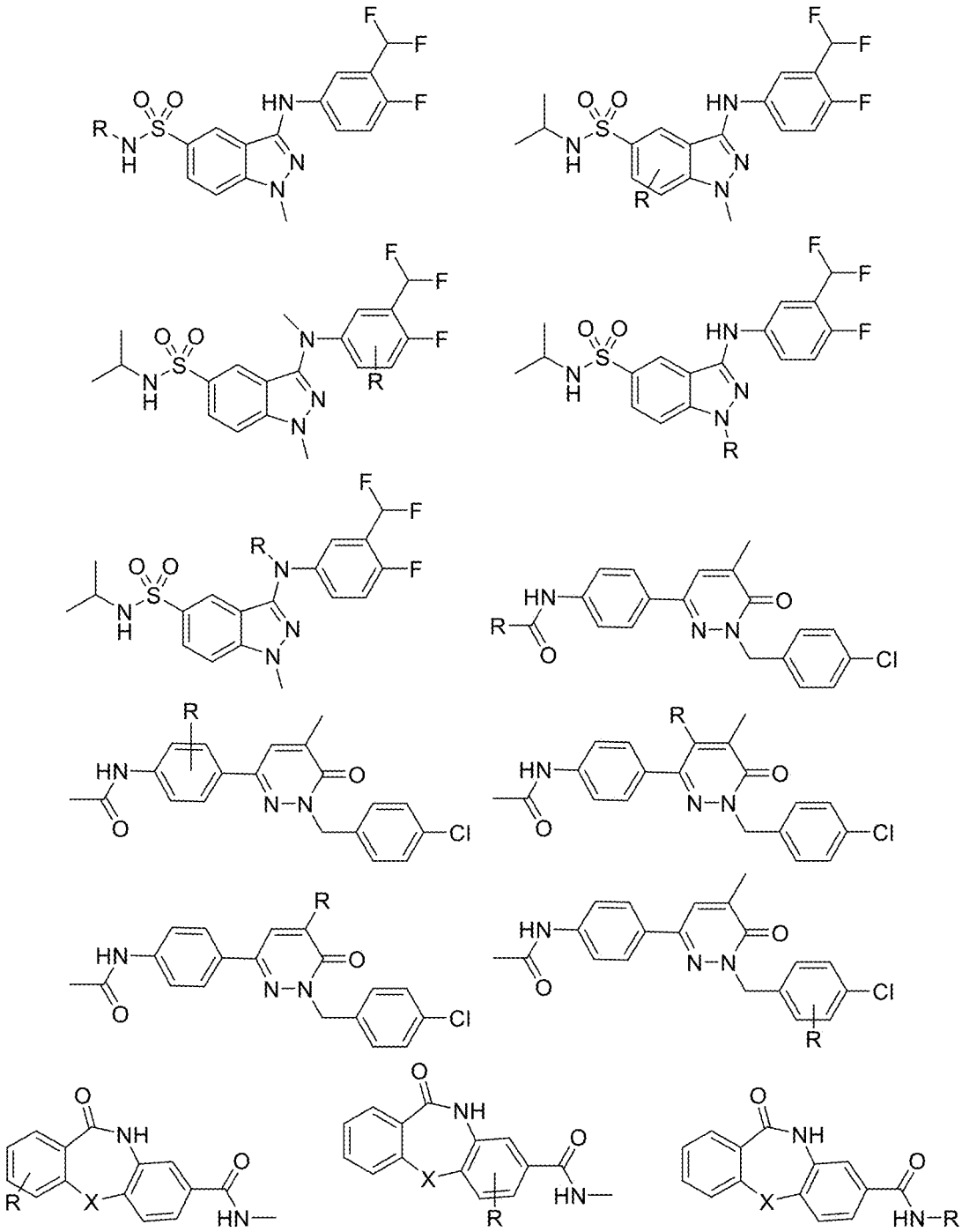


FIG. 8PPPPP

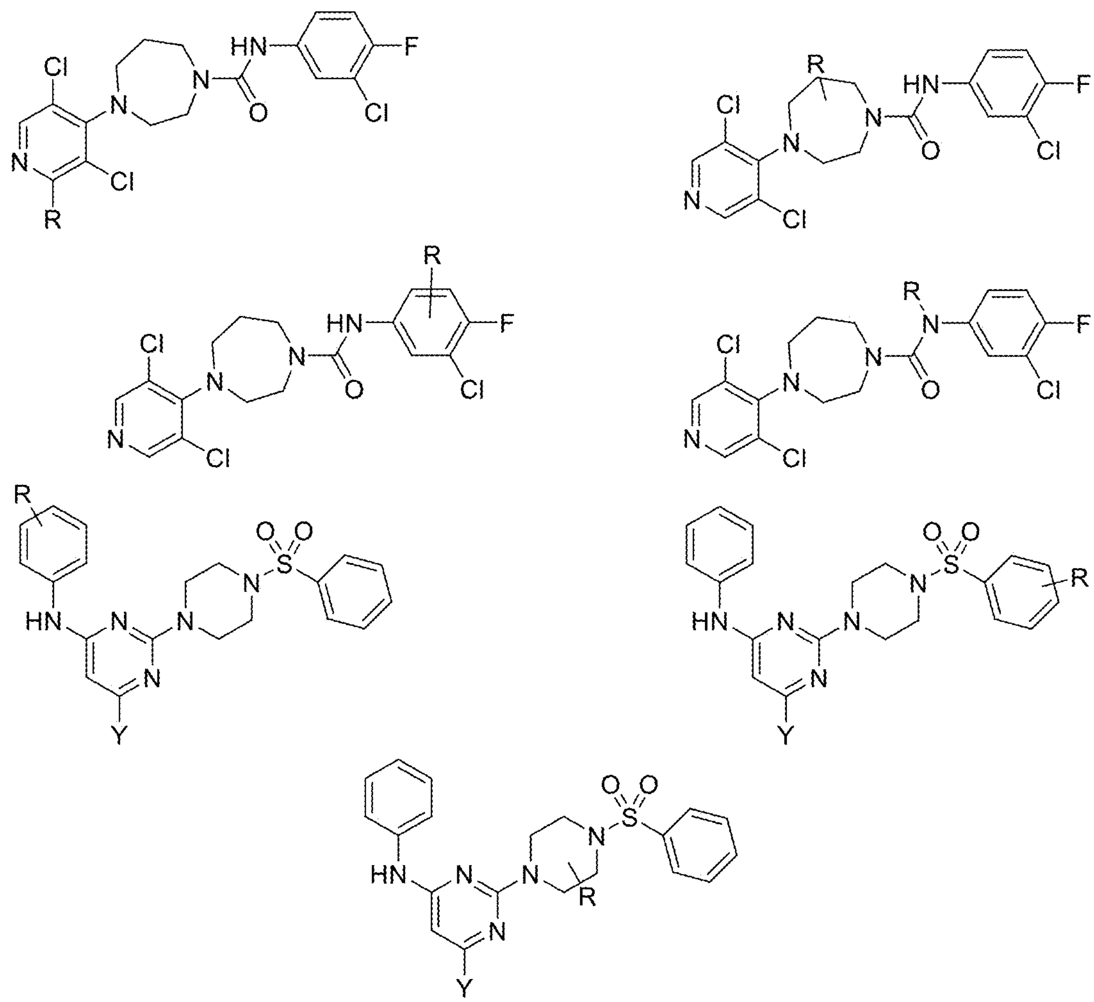
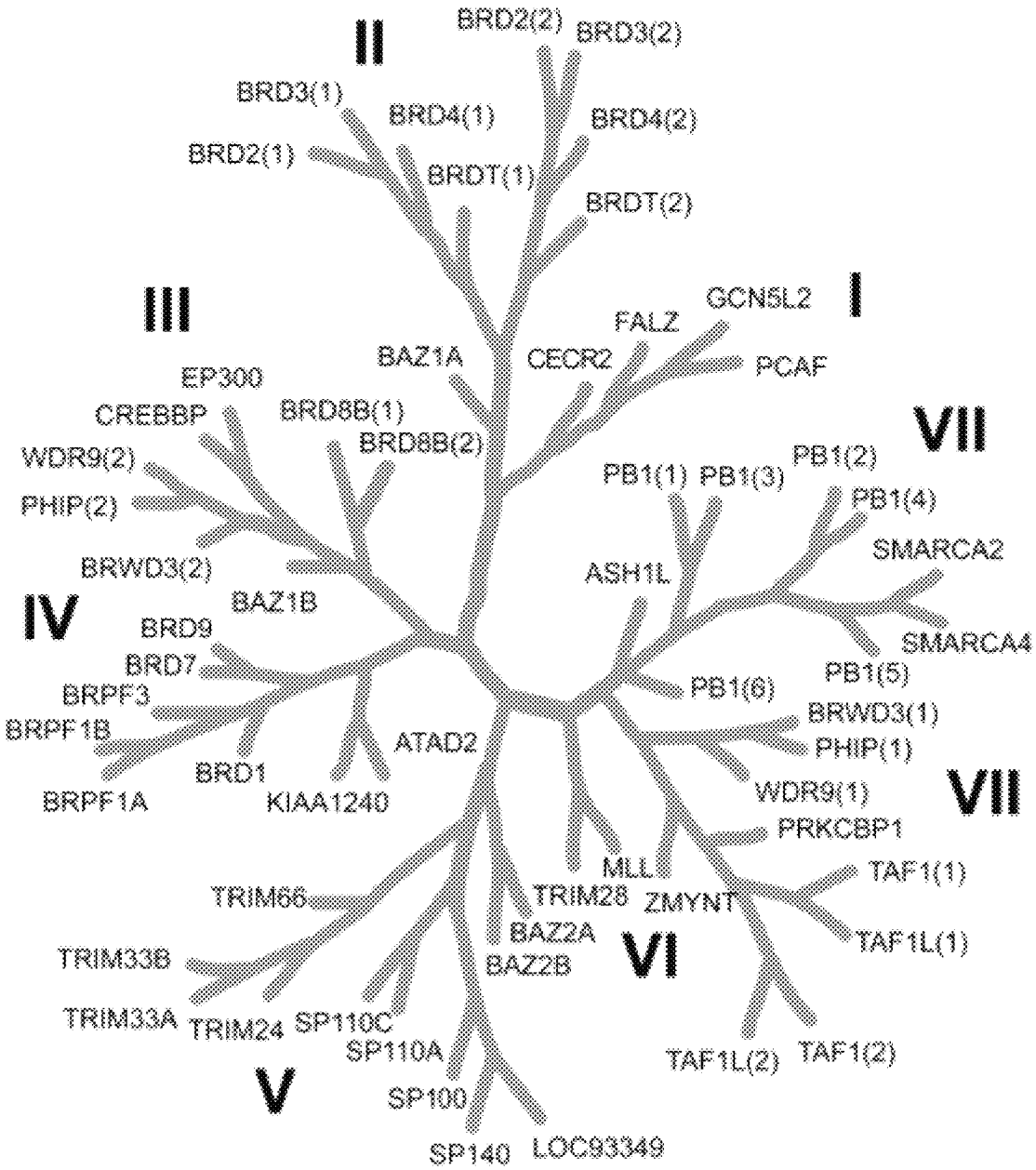


FIG. 9


II
BRD2(2)
BRD3(2)
BRD3(1)
BRD4(1)
BRD4(2)
BRD2(1)
BRDT(1)
BRDT(2)
III
I
GCN5L2
FALZ
BAZ1A
CECR2
PCAF
EP300
CREBBP
BRD8B(1)
BRD8B(2)
VII
WDR9(2)
PHIP(2)
PB1(1)
PB1(3)
PB1(2)
PB1(4)
SMARCA2
BRWD3(2)
ASH1L
IV
BAZ1B
BRD9
SMARCA4
BRD7
PB1(5)
BRPF3
PB1(6)
BRWD3(1)
BRPF1B
ATAD2
PHIP(1)
BRD1
WDR9(1)
VII
BRPF1A
KIAA1240
PRKCBP1
MLL
TAF1(1)
TRIM66
TRIM28
ZMYNT
BAZ2A
TAF1L(1)
TRIM33B
VI
BAZ2B
TRIM33A
TRIM24
SP110C
TAF1L(2)
TAF1(2)
SP110A
V
SP100
SP140
LOC93349

SPIROCYCLIC DEGRONIMERS FOR TARGET PROTEIN DEGRADATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 16/186,334, filed on Nov. 9, 2018, which is a continuation of International Application No. PCT/US2017/032031, filed in the U.S. Receiving Office on May 10, 2017, which claims the benefit of U.S. Provisional Application 62/334,130 which was filed on May 10, 2016. The entirety of these applications are hereby incorporated by reference herein for all purposes.

FIELD OF THE INVENTION

This invention provides compounds that have spirocyclic E3 Ubiquitin Ligase targeting moieties (Degrons), which can be used as is or linked to a targeting ligand for a protein that has been selected for in vivo degradation, and methods of use and compositions thereof as well as methods for their preparation.

BACKGROUND

Protein degradation is a highly regulated and essential process that maintains cellular homeostasis. The selective identification and removal of damaged, misfolded, or excess proteins is achieved via the ubiquitin-proteasome pathway (UPP). The UPP in fact is central to the regulation of almost all cellular processes, including antigen processing, apoptosis, biogenesis of organelles, cell cycling, DNA transcription and repair, differentiation and development, immune response and inflammation, neural and muscular degeneration, morphogenesis of neural networks, modulation of cell surface receptors, ion channels and the secretory pathway, the response to stress and extracellular modulators, ribosome biogenesis and viral infection.

Covalent attachment of multiple ubiquitin molecules by an E3 ubiquitin ligase to a terminal lysine residue marks the protein for proteasome degradation, where the protein is digested into small peptides and eventually into its constituent amino acids that serve as building blocks for new proteins. Defective proteasomal degradation has been linked to a variety of clinical disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, muscular dystrophies, cardiovascular disease, and cancer among others.

There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (*PLOS One,* 2008, 3, 1487) titled "Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling."; Berndsen et al. (*Nat. Struct. Mol. Biol.,* 2014, 21, 301-307) titled "New insights into ubiquitin E3 ligase mechanism"; Deshaies et al. (*Ann. Rev. Biochem.,* 2009, 78, 399-434) titled "RING domain E3 ubiquitin ligases."; Spratt et al. (*Biochem.* 2014, 458, 421-437) titled "RBR E3 ubiquitin ligases: new structures, new insights, new questions."; and Wang et al. (*Nat. Rev. Cancer.,* 2014, 14, 233-347) titled "Roles of F-box proteins in cancer.".

In 1995, Gosink et al. (*Proc. Natl. Acad. Sci. USA* 1995, 92, 9117-9121) in a publication titled "Redirecting the Specificity of Ubiquitination by Modifying Ubiquitin-Conjugating Enzymes", provided proof of concept in vitro that engineered peptides can selectively direct ubiquitination of intracellular proteins. The publication by Nawaz et al. (*Proc. Natl. Acad. Sci. U.S.A.* 1999, 96, 1858-1862) titled "Proteasome-Dependent Degradation of the Human Estrogen Receptor" describes ER degradation which takes advantage of the ubiquitin-proteasome pathway.

Proteinex, Inc. filed a patent application in February 1999 that issued as U.S. Pat. No. 6,306,663 claiming a method of generating a compound for activating the ubiquitination of a Target Protein which comprises covalently linking a Target Protein binding element able to bind specifically to the Target Protein via a ubiquitination recognition element. Proteinex described that the invention can be used to control protein levels in eukaryotes. While the '663 patent may have been based on the first patent application to describe the high level concept of how to manipulate the UPP system to degrade selected proteins in vivo, the patent did not provide sufficient detail to allow persons of skill to easily construct the range of proposed compounds. For example, for the ubiquitination recognition elements, the skilled person was told among other things to use standard methods for drug discovery and screen for appropriate small molecules that would bind to the ligase. Proteinex also emphasized the use of peptides as ubiquitination recognition elements, which can pose significant difficulties for oral drug administration.

Since then, harnessing the ubiquitin-proteasome pathway for therapeutic intervention has received significant interest from the scientific community. The publication by Zhou et al. from Harvard Medical School (*Mol. Cell* 2000, 6, 751-756) titled "Harnessing the Ubiquitination Machinery to Target the Degradation of Specific Cellular Proteins" described an engineered receptor capable of directing ubiquitination in mammalian and yeast cells.

Following from these early publications and others in the mid to late 1990s, it was also recognized by Craig Crews and coworkers (Yale University) that a molecule that is capable of binding a Target Protein and a ubiquitin ligase may cause the Target Protein to be degraded. Their first description of such compounds was provided in U.S. Pat. No. 7,041,298 filed in September 2000 by Deshaies et al. and granted in May 2006 titled "Proteolysis Targeting Chimeric Pharmaceutical", which described a "PROTAC" consisting of a small molecule binder of MAP-AP-2 linked to a peptide capable of binding the F-box protein β-TRCP. Information in the '298 patent is also presented in the corresponding publication by Sakamoto et al. (*Proc. Natl. Acad. Sci. USA* 2001, 98, 8554-8559) titled "Protacs: Chimeric Molecules That Target Proteins to the Skpl-Cullin-F Box Complex for Ubiquitination and Degradation". The publication by Sakamoto et al. (*Mol. Cell. Proteomics* 2003, 2, 1350-1358) titled "Development of Protacs to Target Cancer-Promoting Proteins for Ubiquitination and Degradation" describes an analogous PROTAC (PROTAC2) that instead of degrading MAP-AP-2 degrades estrogen and androgen receptors.

The first E3 ligase successfully targeted with a small molecule was MDM2, which ubiquitinates the tumor suppressor p53. The targeting ligand was an HDM2/MDM2 inhibitor identified in Vassilev et al. (*Science* 2004, 303, 844-848) titled "In Vivo Activation of the P53 Pathway by Small-Molecule Antagonists of MDM2".

Other examples of direct small molecule-induced recruitment of Target Proteins to the proteasome for degradation on addition to cultured cells were described in 2004 (Schneekloth et al. (*J. Am. Chem. Soc.* 2004, 126, 3748-3754) titled "Chemical Genetic Control of Protein Levels: Selective in

Vivo Targeted Degradation"). Schneekloth et al. describe a degradation agent (PROTAC3) that targets the FK506 binding protein (FKBP12) and shows that both PROTAC2 and PROTAC3 hit their respective targets with green fluorescent protein (GFP) imaging. The publication by Schneekloth et al. (*ChemBioChem* 2005, 6, 40-46) titled "Chemical Approaches to Controlling Intracellular Protein Degradation" described the state of the field at the time.

The publication by Schneekloth et al. (*Bioorg. Med. Chem. Lett.* 2008, 18, 5904-5908) titled "Targeted Intracellular Protein Degradation Induced by a Small Molecule: En Route to Chemical Proteomics" describes a degradation agent that consists of two small molecules linked by PEG that in vivo degrades the androgen receptor by concurrently binding the androgen receptor and ubiquitin E3 ligase.

WO 2013/170147 filed by Crews et al. titled "Compounds Useful for Promoting Protein Degradation and Methods of Using Same" describes compounds comprising a protein degradation moiety covalently bound to a linker, wherein the ClogP of the compound is equal to or higher than 1.5. In particular, the specification discloses protein degrading compounds that incorporate certain small molecules that can bind to an E3 ubiquitin ligase.

In unrelated parallel research, scientists were investigating thalidomide toxicity. Ito et al. (*Science* 2010, 327, 1345-1350) titled "Identification of a Primary Target of Thalidomide Teratogenicity", described that cereblon is a thalidomide binding protein. Cereblon forms part of an E3 ubiquitin ligase protein complex which interacts with damaged DNA binding protein 1, forming an E3 ubiquitin ligase complex with Cullin 4 and the E2-binding protein ROC1 (also known as RBX1) where it functions as a substrate receptor to select proteins for ubiquitination. The study revealed that thalidomide-cereblon binding in vivo may be responsible for thalidomide teratogenicity. After the discovery that thalidomide causes teratogenicity in the mid-1960's, the compound and related structures were notwithstanding found to be useful as anti-inflammatory, anti-angiogenic and anti-cancer agents (see Bartlett et al. (*Nat. Rev. Cancer* 2004, 4, 314-322) titled "The Evolution of Thalidomide and Its Imid Derivatives as Anticancer Agents").

The disclosure that thalidomide binds to the cereblon E3 ubiquitin ligase led to research to investigate incorporating thalidomide and certain derivatives into compounds for the targeted destruction of proteins. Two seminal papers were published in *Science in* 2014: G. Lu et al., The Myeloma Drug Lenalidomide Promotes the Cereblon-Dependent Destruction of Ikaros Proteins, *Science,* 343, 305-309 (2014); and J. Kronke et al., Lenalidomide Causes Selective Degradation of IKZF1 and IKZF3 in Multiple Myeloma Cells, *Science,* 343, 301-305 (2014).

U.S. 2014/0356322 assigned to Yale University, GlaxoSmithKline, and Cambridge Enterprise Limited University of Cambridge titled "Compounds and Methods for the Enhanced Degradation of Target Proteins & Other Polypeptides by an E3 Ubiquitin Ligase" describes protein degrading compounds that bind to the VHL E3 Ubiquitin Ligase. See also Buckley et al. (*J. Am. Chem. Soc.* 2012, 134, 4465-4468) titled "Targeting the Von Hippel-Lindau E3 Ubiquitin Ligase Using Small Molecules to Disrupt the Vhl/Hif-lalpha Interaction".

Additional publications in this area include the following: Lu et al. (*Chem. Biol.* 2015, 22, 755-763) titled "Hijacking the E3 Ubiquitin Ligase Cereblon to Efficiently Target Brd4"; Bondeson et al. (*Nat. Chem. Biol.* 2015, 11, 611-617) titled "Catalytic in Vivo Protein Knockdown by Small-Molecule Protacs"; Gustafson et al. (*Angewandte Chemie, International Edition* in English 2015, 54, 9659-9662) titled "Small-Molecule-Mediated Degradation of the Androgen Receptor through Hydrophobic Tagging"; Lai et al. (*Angewandte Chemie, International Edition* in English 2016, 55, 807-810) titled "Modular Protac Design for the Degradation of Oncogenic Bcr-Abl"; Toure et al. (*Angew. Chem. Int. Ed.* 2016, 55, 1966-1973) titled "Small-Molecule Protacs: New Approaches to Protein Degradation"; and Winter et al. (*Science* 2015, 348, 1376-1381) titled "Drug Development. Phthalimide Conjugation as a Strategy for in Vivo Target Protein Degradation" describes thalidomide based Target Protein degradation technology.

WO 2015/160845 assigned to Arvinas Inc. titled "Imide Based Modulators of Proteolysis and Associated Methods of Use" describes protein degradation compounds that incorporate thalidomide and certain derivatives which bind to a cereblon E3 ligase. Additional patent applications filed by Arvinas Inc. directed towards the degradation of a Target Protein using known E3 ligase ligands to direct the Target Protein to the proteasome for degradation include U.S. 2016/0058872 titled "Imide Based Modulators of Proteolysis and Associated Methods of Use"; U.S. 2016/0045607 titled "Estrogen-related Receptor Alpha Based PROTAC Compounds and Associated Methods of Use"; U.S. 2016/0214972 titled "Compounds and Methods for the Targeted Degradation of Androgen Receptor"; U.S. 2016/0272639 titled "Compounds and Methods for the Enhanced Degradation of Target Proteins"; U.S. 2017/0008904 titled "MDM2-Based Modulators of Proteolysis and Associated Methods of Use"; U.S. 2017/0037004 titled "Alanine-Based Modulators of Proteolysis and Associated Methods of Use"; U.S. 2017/0065719 titled "Compounds and Methods for the Targeted Degradation of Bromodomain containing proteins"; WO 2016/036036 titled "Tank Binding Kinase-1 PROTACS and Associated Methods of Use"; and WO 2016/197032 "Imide-Based Modulators and Proteolysis and Associated Methods of Use".

Dana-Farber Cancer Institute has also filed several patent applications directed towards the degradation of a Target Protein using known E3 ligase ligands to direct the Target Protein to the proteasome for degradation. These filings include US 2016/0176916 titled "Methods to Induce Target Protein Degradation through Bifunctional Molecules; WO 2017/024318 titled "Target Protein Degradation to Attenuate Adoptive T-Cell Therapy Associated Adverse Inflammatory Responses"; WO 2017/024317 titled "Methods to Induce Target Protein Degradation through Bifunctional Molecules"; and WO 2017/024319 titled "Tunable Endogenous Protein Degradation".

While progress has been made in the area of modulation of the UPP for in vivo protein degradation, it would be useful to have additional compounds and approaches to more fully harness the UPP for therapeutic treatments.

It is an object of the present invention to provide new compounds, methods, compositions, and methods of manufacture that are useful to degrade selected proteins in vivo.

SUMMARY

Compounds and methods are presented for the treatment of a patient with a disorder that can be treated by protein degradation via the Ubiquitin Proteasomal Pathway (UPP). The invention includes the administration of an effective amount of one or a combination of a spirocyclic "Degrominer" of Formula I or Formula II or the spirocyclic "Degron" of Formula III or IV as described further herein to a patient

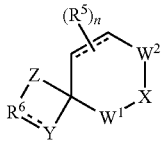
(typically a human) in need thereof, optionally in a pharmaceutically acceptable carrier.

In certain embodiments, the disorder is selected from a benign growth, neoplasm, tumor, cancer, immune disorder, autoimmune disorder, inflammatory disorder, graft-versus-host rejection, viral infection, bacterial infection, an amyloid-based proteinopathy, a proteinopathy, or fibrotic disorder. In a typical embodiment the patient is a human.

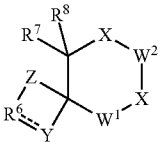
In a first embodiment, the invention provides spirocyclic glutarimide Degrominers of Formula I and II that include a spirocyclic Degron that when covalently linked (Linker) to a ligand (Targeting Ligand) for a Target Protein use the ubiquitin proteasome pathway (UPP) to cause degradation of the Target Protein. This invention thus provides a means for degrading a selected Target Protein even if the protein is not a traditionally druggable target. The Targeting Ligand typically binds non-covalently to the selected Target Protein, and the Degron typically binds non-covalently to an E3 Ligase (for example through a cereblon protein).

The spirocyclic-containing Degronimer of the present invention is a compound of Formula I or Formula II:

(I)



(II)



or a pharmaceutically acceptable salt, N-oxide, isotopic derivative or prodrug, optionally in a pharmaceutically acceptable carrier to create a pharmaceutical composition; wherein:

W^1 is CR^1R^2, C═O, C═S, C═CH_2, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, P(O)NH_2;

W^2 is CR^3R^4, C═O, C═S, C═CH_2, SO_2, S(O), P(O)Oalkyl, P(O)NHalkyl, P(O)N(alkyl)$_2$, P(O)alkyl, P(O)OH, P(O)NH_2;

X is independently NH, NR^{12}, CH_2, CHR^{12}, $C(R^{12})_2$, O, or S;

n is 0, 1, 2, or 3;

=== is a single or double bond;

Y and Z are each independently selected from CH_2, CHR^{12}, $C(R^{12})_2$, C(O), N, NH, NR^{13}, O, S, and S(O) as permitted by valency;

R^1, R^2, R^3, R^4, R^7, and R^8, are independently selected from hydrogen, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclic, hydroxyl, alkoxy, amine, —NHalkyl, or —Nalkyl$_2$;

or R^1 and R^2 form a 3-, 4-, 5-, or 6-membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O;

or R^3 and R^4 form a 3-, 4-, 5-, or 6-membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and 0;

or R^7 and R^8 form a 3-, 4-, 5-, or 6-membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and 0;

or R^1 and R^3 form a 1, 2, 3 or 4 carbon bridged ring;

or R^1 and R^7 form a 1, 2, 3 or 4 carbon bridged ring;

or R^3 and R^7 form a 1, 2, 3, or 4 carbon bridged ring;

in a typical embodiment W^1 is C═O;

in another typical embodiment W^2 is C═O;

in another typical embodiment both W^1 and W^2 are C═O and X is NH;

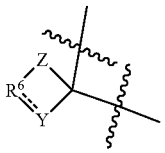
R^5 is selected at each instance from: alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, cyano, aryl, heteroaryl, heteroaliphatic, hetercyclic, —NHalkyl, —N(alkyl)$_2$, —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, aliphatic, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, and haloalkyl;

or two R^5 substituents together with the carbon atom(s) to which they are bound can form a 3, 4, 5 or 6 membered ring;

R^6 is a bond (ie: Y and Z are directly linked to form a 3 membered ring) wherein Y or Z is substituted with R^{10}; or R^6 is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom as long as the resultant molecule has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable, and wherein one of the ring atoms is substituted with R^{10} and the others are optionally substituted with R^{11};

wherein the contiguous atoms of R^6 can be attached through a single or double bond;

or in an alternative embodiment



forms a bicyclic moiety which is substituted with R^{10} and optionally substituted with one or more groups independently selected from R^{11} and oxo;

R^{10} is Linker-Targeting Ligand;

R^{11} is selected at each instance from: hydrogen, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclic, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclic, carbocyclic, alkylamino, alkylhydroxyl, and haloalkyl;

R^{12} is selected from alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic, including alkyl), —C(O)O(aliphatic including alkyl), —NH(aliphatic including alkyl), —N(independently aliphatic including alkyl)$_2$, —$NHSO_2$alkyl, —N(alkyl)SO_2alkyl, —$NHSO_2$aryl, —N(alkyl)SO_2aryl, —$NHSO_2$alkenyl, —N(alkyl)SO_2alkenyl, —$NHSO_2$alkynyl, —N(alkyl)SO_2alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, hetercyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, and haloalkyl;

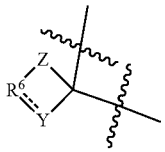
R^{13} is selected from alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, and —C(O)Oalkyl;

Linker is a chemical group that attaches the Degron to a Targeting Ligand.

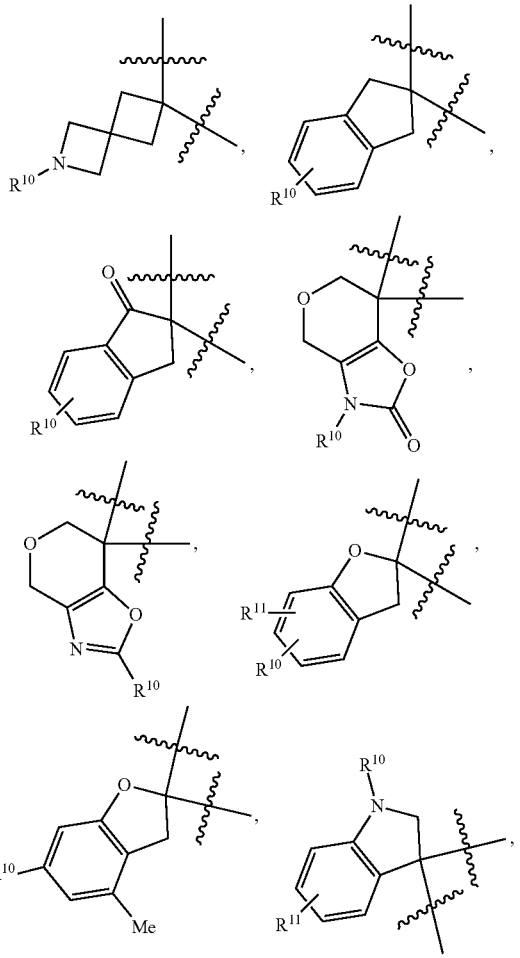
Targeting Ligand is a moiety that is capable of binding to or binds to a targeted protein, and wherein the targeted protein is a mediator of disease in a host, as described in more detail below with non-limiting examples in the Figures.

The selected Target Protein is derived from a gene that has undergone an amplification, translocation, deletion, or inversion event which causes or is caused by a medical disorder. In certain aspects, the selected Target Protein has been post-translationally modified by one, or combinations, of phosphorylation, acetylation, acylation including propionylation and crotylation, N-linked glycosylation, amidation, hydroxylation, methylation, poly-methylation, O-linked glycosylation, pyrogultamoylation, myristoylation, farnesylation, geranylgeranylation, ubiquitination, sumoylation, or sulfation which causes or is caused by a medical disorder. In an alternative embodiment, the Target Protein is covalently modified by a Targeting Ligand that has been functionalized to produce a degrader, and the covalent ligand can be irreversible or reversible.

Non-limiting examples of bicyclic



moieties include:



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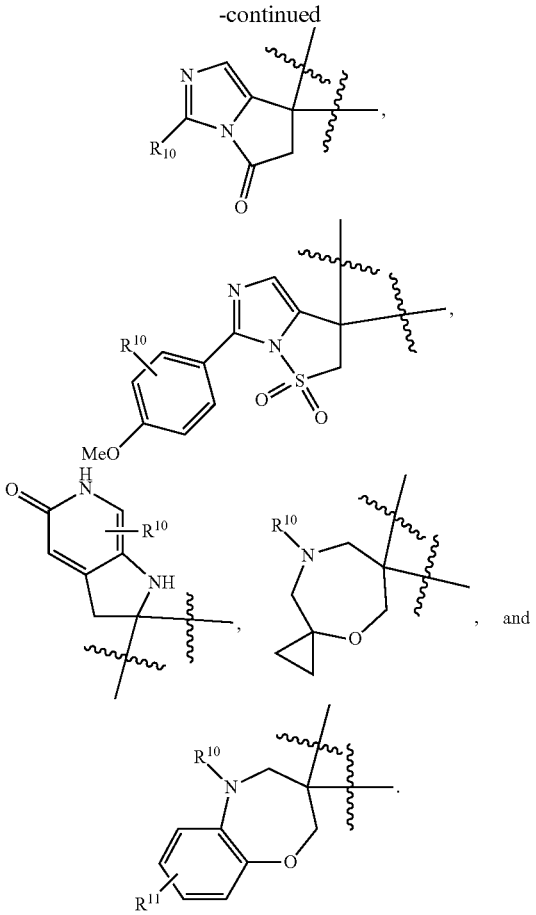


Formula I and Formula II are novel bifunctional compounds with spirocyclic E3 Ubiquitin Ligase targeting moieties (Degrons) linked to Targeting Ligands (described in more detail below), which function to recruit a selected Targeted Protein to E3 Ubiquitin Ligase for degradation.

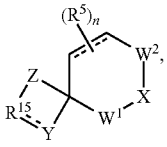
In Formula I and Formula II, the spirocyclic moiety is covalently linked to a Targeted Protein ligand through a Linker which can be of varying length and functionality, as described in detail herein. In one embodiment, the spirocyclic Degron moiety is linked directly to the Targeting Ligand (i.e., the Linker is a bond). In certain embodiments, the Linker can be any chemically stable group that attaches the spirocyclic Degron to the Targeting Ligand. In a typical embodiment the Linker has a chain of 2 to 14, 15, 16, 17, 18 or 20 or more carbon atoms of which one or more carbons can be replaced by a heteroatom such as O, N, S, P, as long as the resulting molecule has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable. In certain embodiments the chain has 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 contiguous atoms in the chain. For example, the chain may include 1 or more ethylene glycol units, and in some embodiments, may have at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more contiguous, partially contiguous or non-contiguous ethylene glycol units in the Linker. In certain embodiments the chain has at least 1, 2, 3, 4, 5, 6, 7, or 8 branches which can be independently alkyl, heteroalkyl, aryl, heteroaryl, alkenyl, or alkynyl substituents, which in one embodiment, each branch has 10, 8, 6, 4, 3, 2 carbons or one carbon.

In one embodiment, a pharmaceutical formulation comprising a therapeutically effective amount of a spirocyclic Degronimer of Formula I or Formula II or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier is provided.

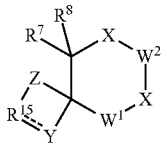
In another aspect of the invention, a spirocyclic Degron of Formula III or IV is provided that binds to cereblon in vivo and is thus useful to treat a disorder that can be ameliorated by inhibiting the E3 Ligase that cereblon is a protein subunit of. The spirocyclic Degron of Formula III or IV, or a pharmaceutically acceptable salt thereof, can be administered in an effective amount for those indications known for the cereblon binders thalidomide, pomalidomide and lenalidomide.

The present invention thus includes a spirocyclic Degron of Formula III or Formula IV:

(III)



(IV)



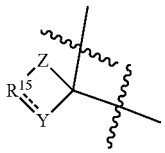
or a pharmaceutically acceptable salt, N-oxide, isotopic derivative or prodrug, optionally in a pharmaceutically acceptable carrier to create a pharmaceutical composition;

wherein:

R^{15} is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom as long as the resultant molecule has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable, and wherein the ring atoms are optionally substituted with R^{11};

wherein the contiguous atoms of R^{15} can be attached through a single or double bond;

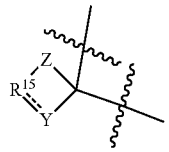
or in an alternative embodiment



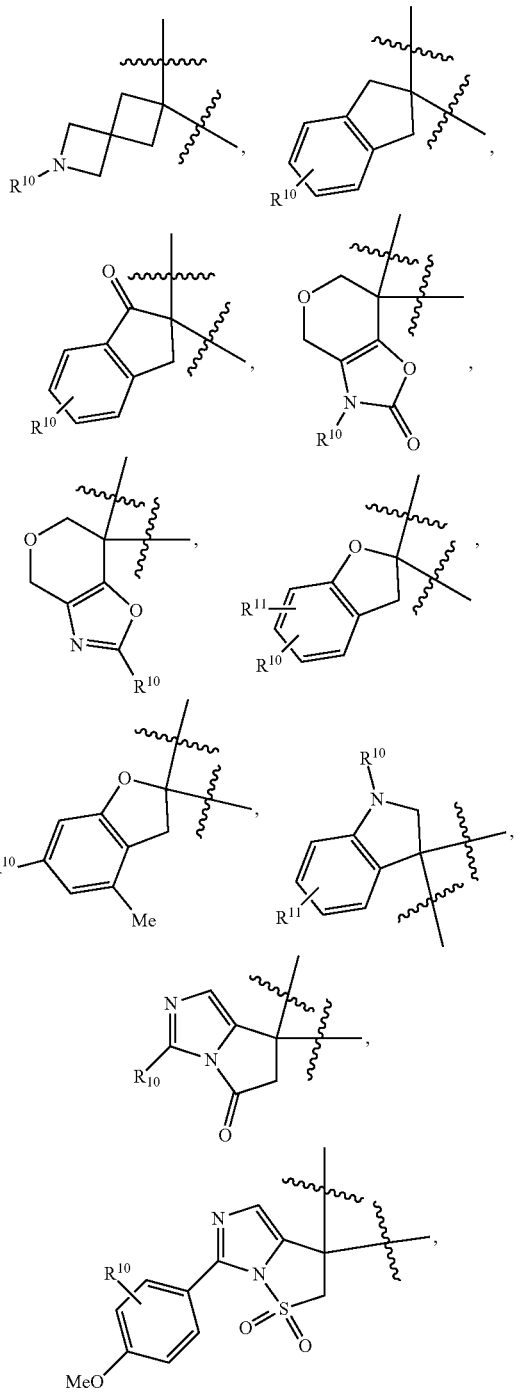
forms a bicyclic moiety which is optionally substituted with one or more groups independently selected from R^{11} and oxo;

and the other variables are as defined above.

Non-limiting examples of bicyclic



moieties include:



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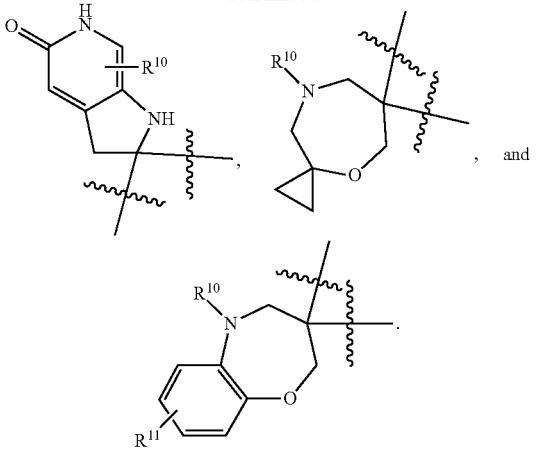

The spirocyclic compounds of Formulas III and IV do not include a Linker or a Targeting Ligand. These Formula III and IV compounds are useful as therapeutic agents when administered in an effective amount to a host, including a human, for the treatment of a medical disorder including, but not limited to, those disorders that are treatable with thalidomide, pomalidomide and lenalidomide. Examples include abnormal cellular proliferation, including a tumor or cancer, or a myelo- or lymphoproliferative disorder such as B- or T-cell lymphomas, multiple myeloma, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, or a post-transplant lymphoproliferative disorder; an immune disorder, including autoimmune disorders for example, Addison disease, Celiac disease, dermatomyositis, Graves disease, thyroiditis, multiple sclerosis, pernicious anemia, reactive arthritis, lupus, or type I diabetes; a disease of cardiovascular malfunction, including hypercholesterolemia; an infectious disease, including viral and/or bacterial infections; an inflammatory condition, including asthma, chronic peptic ulcers, tuberculosis, rheumatoid arthritis, periodontitis, ulcerative colitis, Crohn's disease, and hepatitis.

In certain embodiments, the present invention thus provides the administration of an effective amount of a compound of Formula I or II to treat a patient, for example, a human, having an infectious disease, wherein the therapy targets a Target Protein of the infectious agent or the host (Formulas I and II), or acts via binding to cereblon or its E3 ligase (Formulas III and IV) optionally in combination with another bioactive agent. The disease state or condition may be caused by a microbial agent or other exogenous agent such as a virus (as non-limiting examples, HIV, HBV, HCV, HSV, HPV, RSV, CMV, Ebola, Flavivirus, Pestivirus, Rotavirus, Influenza, Coronavirus, EBV, viral pneumonia, drug-resistant viruses, Bird flu, RNA virus, DNA virus, adenovirus, poxvirus, Picornavirus, Togavirus, Orthomyxovirus, Retrovirus or Hepadnovirus), bacteria (including but not limited to Gram-negative, Gram-positive, Atypical, *Staphylococcus, Streptococcus, E. Coli, Salmonella, Helicobacter pylori*, meningitis, gonorrhea, Chlamydiaceae, Mycoplasmataceae, etc), fungus, protozoa, helminth, worms, prion, parasite, or other microbe.

In certain embodiments, the compound of Formula I, Formula II, Formula III or Formula IV has at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched. In one embodiment, the compound of Formula I, Formula II, Formula III or Formula IV includes a deuterium or multiple deuterium atoms.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present application, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the present application will be apparent from the following detailed description and claims.

The present invention thus includes at least the following features:

(a) A spirocyclic compound of Formula I, Formula II, Formula III, or Formula IV as described herein, and pharmaceutically acceptable salts, isotopic derivative (including a deuterated derivative) and prodrugs thereof;

(b) A spirocyclic compound of Formula I or Formula II, for the treatment of a disorder that is mediated by a Targeted Protein, wherein the compound includes a Targeting Ligand for the Targeted Protein, and wherein the spirocyclic compound is optionally linked to the Targeting Ligand through a Linker;

(c) Use of a compound of Formula I or Formula II in an effective amount in the treatment of a patient, including a human, with a disorder mediated by a Targeted Protein, including abnormal cellular proliferation such as a tumor or cancer, an immune disorder, an autoimmune disorder or inflammatory disorder, a cardiovascular disorder, an infectious disease, or other disorder that responds to such treatment;

(d) Use of a compound of Formula III or Formula IV or a pharmaceutically acceptable salt thereof in an effective amount, in the treatment of a patient, including a human, with a medical disorder as described herein, for example, with abnormal cellular proliferation such as a tumor or cancer, an autoimmune disorder or inflammatory disorder, a cardiovascular disorder, an infectious disease, or other disorder that responds to such treatment;

(e) Use of a compound of Formula I, Formula II, Formula III, or Formula IV, and pharmaceutically acceptable salts, isotopic derivatives, and prodrugs thereof in the manufacture of a medicament for the treatment of a medical disorder;

(f) A method for manufacturing a medicament intended for the therapeutic treatment of a disorder characterized in that a compound of Formula I, Formula II, Formula III, or Formula IV as described herein is used in the manufacture;

(g) A compound of Formula I, Formula II, Formula III, or Formula IV as described herein, and pharmaceutically acceptable salts and prodrugs thereof that are useful in the treatment of an abnormal cellular proliferation such as cancer, including any of the cancers described herein;

(h) Use of a compound of Formula I, Formula II, Formula III, or Formula IV and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for the treatment of an abnormal cellular proliferation such as cancer, including any of the cancers described herein;

(i) A method for manufacturing a medicament intended for the therapeutic use of treating an abnormal cellular proliferation such as cancer, including any of the cancers described herein, characterized in that a compound of For-

mula I, Formula II, Formula III, or Formula IV as described herein is used in the manufacture;

(j) A compound of Formula I, Formula II, Formula III, or Formula IV as described herein, and pharmaceutically acceptable salts, isotopic derivatives and prodrugs thereof that are useful in the treatment of a tumor, including any of the tumors described herein;

(k) Use of a compound of Formula I, Formula II, Formula III, or Formula IV, and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for the treatment of a tumor, including any of the tumors described herein;

(l) A method for manufacturing a medicament intended for the therapeutic use of treating a tumor, including any of the tumors described herein, characterized in that a compound of Formula I, Formula II, Formula III, or Formula IV as described herein is used in the manufacture;

(m) A compound of Formula I, Formula II, Formula III or Formula IV as described herein, and pharmaceutically acceptable salts and prodrugs thereof that are useful in the treatment of an immune, autoimmune or inflammatory disorder;

(n) Use of a compound of Formula I, Formula II, Formula III or Formula IV and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for the treatment of an immune, autoimmune or inflammatory disorder;

(o) A method for manufacturing a medicament intended for the therapeutic use of treating an immune, autoimmune or inflammatory disorder, characterized in that a compound of Formula I, Formula II, Formula III or Formula IV as described herein is used in the manufacture;

(p) A compound of Formula I, Formula II, Formula III or Formula IV as described herein, and pharmaceutically acceptable salts and prodrugs thereof that are useful in the treatment of an infection, including but not limited to a viral infection, for example, HIV, HBV, HCV and RSV;

(q) Use of a compound of Formula I, II, III or IV and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for the treatment of an infection, including but not limited to a viral infection, such as HIV, HBV, HCV and RSV;

(r) A method for manufacturing a medicament intended for the therapeutic use of treating an infection such as a viral infection including but not limited to HIV, HBV, HCV and RSV, characterized in that a compound of Formula I, II, III or IV as described herein is used in the manufacture;

(s) A pharmaceutical formulation comprising an effective host-treating amount of the compound of Formula I, Formula II, Formula III, or Formula IV or a pharmaceutically acceptable salt or prodrug thereof together with a pharmaceutically acceptable carrier or diluent;

(t) A compound of Formula I, Formula II, Formula III, or Formula IV as described herein as a mixture of enantiomers or diastereomers (as relevant), including as a racemate;

(u) A compound of Formula I, Formula II, Formula III, or Formula IV as described herein in enantiomerically or diastereomerically (as relevant) enriched form, including as an isolated enantiomer or diastereomer (i.e., greater than 85, 90, 95, 97 or 99% pure); and,

(v) A process for the preparation of therapeutic products that contain an effective amount of a compound of Formula I, Formula II, Formula III, or Formula IV, as described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**A-**1**C present examples of Retenoid X Receptor (RXR) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**D-**1**F present examples of general Dihydrofolate reductase (DHFR) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**G presents examples of *Bacillus anthracis* Dihydrofolate reductase (BaDHFR) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**H-**1**J present examples of Heat Shock Protein 90 (HSP90) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**K-**1**Q present examples of General Kinase and Phosphatase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**R-**1**S present examples of Tyrosine Kinase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**T presents examples of Aurora Kinase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**U presents examples of Protein Tyrosine Phosphatase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**V presents examples of ALK Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**W presents examples of ABL Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**X presents examples of JAK2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**Y-**1**Z present examples of MET Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**AA presents examples of mTORC1 and/or mTORC2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**BB-**1**CC present examples of Mast/stem cell growth factor receptor (SCFR), also known as c-KIT receptor, Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**DD presents examples of IGF1R and/or IR Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**EE-**1**FF present examples of HDM2 and/or MDM2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**GG-**1**MM present examples of BET Bromodomain-Containing Protein Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**NN presents examples of HDAC Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**OO presents examples of RAF Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**PP presents examples of FKBP Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**QQ-**1**TT present examples of Androgen Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**UU presents examples of Estrogen Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**VV-**1**WW present examples of Thyroid Hormone Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **1**XX presents examples of HIV Protease Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1YY presents examples of HIV Integrase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1ZZ presents examples of HCV Protease Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1AAA presents examples of AP1 and/or AP2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1BBB-1CCC present examples of MCL-1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1DDD presents examples of IDH1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1EEE-1FFF present examples of RAS or RASK Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1GGG presents examples of MERTK or MER Targeting Ligands wherein R is the point at which the linker is attached.

FIG. 1HHH-1III present examples of EGFR Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1JJJ-1KKK present examples of FLT3 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 1LLL presents examples of SMRCA2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2A presents examples of the kinase inhibitor Targeting Ligands U09-CX-5279 (derivatized) wherein R is the point at which the Linker is attached.

FIG. 2B-2C present examples of kinase inhibitor Targeting Ligands, including the kinase inhibitor compounds Y1W and Y1X (derivatized) wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the kinase inhibitors identified in Millan et al. "Design and Synthesis of Inhaled P38 Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease" *J Med. Chem.,* 54: 7797 (2011).

FIG. 2D presents examples of kinase inhibitor Targeting Ligands, including the kinase inhibitor compounds 6TP and 0TP (derivatized) wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the kinase inhibitors identified in Schenkel et al. "Discovery of Potent and Highly Selective Thienopyridine Janus Kinase 2 Inhibitors" *J. Med. Chem.,* 54 (24): 8440-8450 (2011).

FIG. 2E presents examples of kinase inhibitor Targeting Ligands, including the kinase inhibitor compound 07U wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the kinase inhibitors identified in Van Eis et al. "2 6-Naphthyridines as potent and selective inhibitors of the novel protein kinase C isozymes" *Biorg. Med. Chem. Lett.,* 21(24): 7367-72 (2011).

FIG. 2F presents examples of kinase inhibitor Targeting Ligands, including the kinase inhibitor compound YCF, wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the kinase inhibitors identified in Lountos et al. "Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2) a Drug Target for Cancer Therapy" *J. Struct. Biol.,* 176: 292 (2011).

FIG. 2G-2H present examples of kinase inhibitor Targeting Ligands, including the kinase inhibitors XK9 and NXP (derivatized) wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the kinase inhibitors identified in Lountos et al. "Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2) a Drug Target for Cancer Therapy" *J. Struct. Biol.,* 176: 292 (2011).

FIG. 2I-2J present examples of kinase inhibitor Targeting Ligands wherein R is the point at which the Linker r is attached.

FIG. 2K-2M present examples of Cyclin Dependent Kinase 9 (CDK9) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Baumli et al. "The structure of P-TEFb (CDK9/cyclin Ti) its complex with flavopiridol and regulation by phosphorylation." *Embo J.,* 27: 1907-1918 (2008); Bettayeb et al. "CDK Inhibitors Roscovitine and CR8 Trigger Mcl-1 Down-Regulation and Apoptotic Cell Death in Neuroblastoma Cells." *Genes Cancer,* 1: 369-380 (2010); Baumli et al. "Halogen bonds form the basis for selective P-TEFb inhibition by DRB." *Chem. Biol.* 17: 931-936 (2010); Hole et al. "Comparative Structural and Functional Studies of 4-(Thiazol-5-Yl)-2-(Phenylamino)Pyrimidine-5-Carbonitrile Cdk9 Inhibitors Suggest the Basis for Isotype Selectivity." *J. Med. Chem.* 56: 660 (2013); Luicking et al. "Identification of the potent and highly selective PTEFb inhibitor BAY 1251152 for the treatment of cancer—From p.o. to i.v. application via scaffold hops." Licking et al. U. AACR Annual Meeting, Apr. 1-5, 2017 Washington, D.C. USA.

FIG. 2N-2P present examples of Cyclin Dependent Kinase 4/6 (CDK4/6) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Lu H.; Schulze-Gahmen U.; "Toward understanding the structural basis of cyclin-dependent kinase 6 specific inhibition." *J. Med. Chem.,* 49: 3826-3831 (2006); 4-(Pyrazol-4-yl)-pyrimidines as selective inhibitors of cyclin-dependent kinase 4/6. Cho et al. (2010) J. Med. Chem. 53: 7938-7957; Cho Y. S. et al. "Fragment-Based Discovery of 7-Azabenzimidazoles as Potent Highly Selective and Orally Active CDK4/6 Inhibitors." *ACS Med Chem Lett* 3: 445-449 (2012); Li Z. et al. "Discovery of AMG 925 a FLT3 and CDK4 dual kinase inhibitor with preferential affinity for the activated state of FLT3." *J. Med. Chem.* 57: 3430-3449 (2014); Chen P. et al. "Spectrum and Degree of CDK Drug Interactions Predicts Clinical Performance." *Mol. Cancer Ther.* 15: 2273-2281 (2016).

FIG. 2Q presents examples of Cyclin Dependent Kinase 12 and/or Cyclin Dependent Kinase 13 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Zhang T. et al. "Covalent Targeting of Remote Cysteine Residues to Develop Cdk12 and Cdk13 Inhibitors." *Nat. Chem. Biol.* 12: 876 (2016).

FIG. 2R-2S present examples of Glucocorticoid Receptor Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2T-2U present examples of RasG12C Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2V presents examples of Her3 Targeting Ligands wherein R is the point at which the Linker is attached and R' is

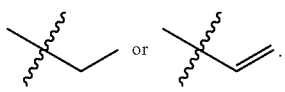

FIG. 2W presents examples of Bcl-2 or Bcl-XL Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2X-2NN present examples of BCL2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Toure B. B. et al. "The role of the acidity of N-heteroaryl sulfonamides as inhibitors of bcl-2 family protein-protein interactions." *ACS Med Chem Lett,* 4: 186-190 (2013); Porter J. et al. "Tetrahydroisoquinoline Amide Substituted Phenyl Pyrazoles as Selective Bcl-2 Inhibitors" *Bioorg. Med. Chem. Lett.* 19: 230 (2009); Souers A. J. et al. "ABT-199 a potent and selective BCL-2 inhibitor achieves antitumor activity while sparing platelets." Nature Med. 19: 202-208 (2013); Angelo Aguilar et al. "A Potent and Highly Efficacious Bcl-2/Bcl-xL Inhibitor" *J Med Chem.* 56(7): 3048-3067 (2013); Longchuan Bai et al. "BM-1197: A Novel and Specific Bcl-2/Bcl-xL Inhibitor Inducing Complete and Long-Lasting Tumor Regression In Vivo" *PLoS ONE* 9(6): e99404; Fariba Ne'matil et al. "Targeting Bcl-2/Bcl-XL Induces Antitumor Activity in Uveal Melanoma Patient-Derived Xenografts" *PLoS ONE* 9(1): e80836; WO2015011396 titled "Novel derivatives of indole and pyrrole method for the production thereof and pharmaceutical compositions containing same"; WO2008060569A1 titled "Compounds and methods for inhibiting the interaction of Bcl proteins with binding partners"; "Inhibitors of the anti-apoptotic Bcl-2 proteins: a patent review" *Expert Opin. Ther. Patents* 22(1):2008 (2012); and, Porter et al. "Tetrahydroisoquinoline amide substituted phenyl pyrazoles as selective Bcl-2 inhibitors" *Bioorg Med Chem Lett.,* 19(1): 230-3 (2009).

FIG. 2OO-2UU present examples of BCL-XL Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Zhi-Fu Tao et al. "Discovery of a Potent and Selective BCL-XL Inhibitor with in Vivo Activity" *ACSMed. Chem. Lett.,* 5: 1088-1093 (2014); Joel D. Leverson et al. "Exploiting selective BCL-2 family inhibitors to dissect cell survival dependencies and define improved strategies for cancer therapy" *Science Translational Medicine,* 7:279ra40 (2015); and, the crystal structure PDB 3ZK6 (Guillaume Lessene et al. "Structure-guided design of a selective BCL-XL inhibitor" *Nature Chemical Biology* 9: 390-397 (2013))

FIG. 2VV presents examples of PPAR-gamma Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2WW-2YY present examples of EGFR Targeting Ligands that target the EGFR L858R mutant, including erlotinib, gefitnib, afatinib, neratinib, and dacomitinib, wherein R is the point at which the Linker is attached.

FIG. 2ZZ-2FFF present examples of EGFR Targeting Ligands that target the EGFR T790M mutant, including osimertinib, rociletinib, olmutinib, naquotinib, nazartinib, PF-06747775, Icotinib, Neratinib Avitinib, Tarloxotinib, PF-0645998, Tesevatinib, Transtinib, WZ-3146, WZ8040, and CNX-2006, wherein R is the point at which the Linker is attached.

FIG. 2GGG presents examples of EGFR Targeting Ligands that target the EGFR C797S mutant, including EAI045, wherein R is the point at which the Linker is attached.

FIG. 2HHH presents examples of BCR-ABL Targeting Ligands that target the BCR-ABL T315I mutantm including Nilotinib and Dasatinib, wherein R is the point at which the Linker is attached. See for example, the crystal structure PDB 3CS9.

FIG. 2III presents examples of Targeting Ligands that target BCR-ABL, including Nilotinib, Dasatinib Ponatinib and Bosutinib, wherein R is the point at which the Linker is attached.

FIG. 2JJJ-2KKK present examples of ALK Targeting Ligands that target the ALK L1196M mutant including Ceritinib, wherein R is the point at which the Linker is attached. See for example, the crystal structure PDB 4MKC.

FIG. 2LLL presents examples of JAK2 Targeting Ligands that target the JAK2V617F mutant, including Ruxolitinib, wherein R is the point at which the Linker is attached.

FIG. 2MMM presents examples of BRAF Targeting Ligands that target the BRAF V600E mutant including Vemurafenib, wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PBD 3OG7.

FIG. 2NNN presents examples of BRAF Targeting Ligands, including Dabrafenib, wherein R is the point at which the Linker is attached.

FIG. 2OOO presents examples of LRRK2 Targeting Ligands that target the LRRK2 R1441C mutant wherein R is the point at which the Linker is attached.

FIG. 2PPP presents examples of LRRK2 Targeting Ligands that target the LRRK2 G2019S mutant wherein R is the point at which the Linker is attached.

FIG. 2QQQ presents examples of LRRK2 Targeting Ligands that target the LRRK2 I2020T mutant wherein R is the point at which the Linker is attached.

FIG. 2RRR-2TTT present examples of PDGFRa Targeting Ligands that target the PDGFRα T674I mutant, including AG-1478, CHEMBL94431, Dovitinib, erlotinib, gefitinib, imatinib, Janex 1, Pazopanib, PD153035, Sorafenib, Sunitinib, and WHI-P180, wherein R is the point at which the Linker is attached.

FIG. 2UUU presents examples of RET Targeting Ligands that target the RET G691S mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2VVV presents examples of RET Targeting Ligands that target the RET R749T mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2WWW presents examples of RET Targeting Ligands that target the RET E762Q mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2XXX presents examples of RET Targeting Ligands that target the RET Y791F mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2YYY presents examples of RET Targeting Ligands that target the RET V804M mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2ZZZ presents examples of RET Targeting Ligands that target the RET M918T mutant, including tozasertib, wherein R is the point at which the Linker is attached.

FIG. 2AAAA presents examples of Fatty Acid Binding Protein Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2BBBB presents examples of 5-Lipoxygenase Activating Protein (FLAP) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2CCCC presents examples of Kringle Domain V 4BVV Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2DDDD presents examples of Lactoylglutathione Lyase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. 2EEEE-2FFFF present examples of mPGES-1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**GGGG-**2**JJJJ present examples of Factor Xa Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Maignan S. et al. "Crystal structures of human factor Xa complexed with potent inhibitors." *J. Med. Chem.* 43: 3226-3232 (2000); Matsusue T. et al. "Factor Xa Specific Inhibitor that Induces the Novel Binding Model in Complex with Human Fxa." (to be published); the crystal structures PDB liqh, liqi, liqk, and liqm; Adler M. et al. "Crystal Structures of Two Potent Nonamidine Inhibitors Bound to Factor Xa." *Biochemistry* 41: 15514-15523 (2002); Roehrig S. et al. "Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-Oxo-3-[4-(3-Oxomorpholin-4-Yl)Phenyl]-1 3-Oxazolidin-5-Yl}Methyl)Thiophene-2-Carboxamide (Bay 59-7939): An Oral Direct Factor Xa Inhibitor." *J. Med. Chem.* 48: 5900 (2005); Anselm L. et al. "Discovery of a Factor Xa Inhibitor (3R 4R)-1-(2 2-Difluoro-Ethyl)-Pyrrolidine-3 4-Dicarboxylic Acid 3-[(5-Chloro-Pyridin-2-Yl)-Amide] 4-{[2-Fluoro-4-(2-Oxo-2H-Pyridin-1-Yl)-Phenyl]-Amide} as a Clinical Candidate." *Bioorg. Med. Chem.* 20: 5313 (2010); and, Pinto D. J. et al. "Discovery of 1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4 5 6 7-tetrahydro-1H-pyrazolo[3 4-c]pyridine-3-carboxamide (Apixaban BMS-562247) a Highly Potent Selective Efficacious and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa." *J. Med. Chem.* 50: 5339-5356 (2007).

FIG. **2**KKKK presents examples of Kallikrein 7 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Maibaum J. et al. "Small-molecule factor D inhibitors targeting the alternative complement pathway." *Nat. Chem. Biol.* 12: 1105-1110 (2016).

FIG. **2**LLLL-**2**MMMM present examples of Cathepsin K Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Rankovic Z. et al. "Design and optimization of a series of novel 2-cyano-pyrimidines as cathepsin K inhibitors" *Bioorg. Med. Chem. Lett.* 20: 1524-1527 (2010); and, Cai J. et al. "Trifluoromethylphenyl as P2 for ketoamide-based cathepsin S inhibitors." *Bioorg. Med. Chem. Lett.* 20: 6890-6894 (2010).

FIG. **2**NNNN presents examples of Cathepsin L Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Kuhn B. et al. "Prospective Evaluation of Free Energy Calculations for the Prioritization of Cathepsin L Inhibitors." *J. Med. Chem.* 60: 2485-2497 (2017).

FIG. **2**OOOO presents examples of Cathepsin S Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Jadhav P. K. et al. "Discovery of Cathepsin S Inhibitor LY3000328 for the Treatment of Abdominal Aortic Aneurysm" *ACS Med. Chem. Lett.* 5: 1138-1142." (2014).

FIG. **2**PPPP-**2**SSSS present examples of MTH1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Kettle J. G. et al. "Potent and Selective Inhibitors of Mth1 Probe its Role in Cancer Cell Survival." *J. Med. Chem.* 59: 2346 (2016); Huber K. V. M. et al. "Stereospecific Targeting of Mth1 by (S)-Crizotinib as an Anticancer Strategy." *Nature* 508: 222 (2014); Gad H. et al. "MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool." *Nature* 508: 215-221 (2014); Nissink J. W. M. et al. "Mth1 Substrate Recognition—an Example of Specific Promiscuity." *Plos One* 11: 51154 (2016); and, Manuel Ellermann et al. "Novel class of potent and selective inhibitors efface MTH1 as broad-spectrum cancer target." AACR National Meeting Abstract 5226, 2017.

FIG. **2**TTTT-**2**ZZZZ present examples of MDM2 and/or MDM4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Popowicz G. M. et al. "Structures of low molecular weight inhibitors bound to MDMX and MDM2 reveal new approaches for p53-MDMX/MDM2 antagonist drug discovery." *Cell Cycle,* 9 (2010); Miyazaki M. et al. "Synthesis and evaluation of novel orally active p53-MDM2 interaction inhibitors." *Bioorg. Med. Chem.* 21: 4319-4331 (2013); Miyazaki M. et al. "Discovery of DS-5272 as a promising candidate: A potent and orally active p53-MDM2 interaction inhibitor." *Bioorg Med Chem.* 23: 2360-7 (2015); Holzer P. et al. "Discovery of a Dihydroisoquinolinone Derivative (NVP-CGM097): A Highly Potent and Selective MDM2 Inhibitor Undergoing Phase 1 Clinical Trials in p53 wt Tumors." *J. Med. Chem.* 58: 6348-6358 (2015); Gonzalez-Lopez de Turiso F. et al. "Rational Design and Binding Mode Duality of MDM2-p53 Inhibitors." J. Med. Chem. 56: 4053-4070 (2013); Gessier F. et al. "Discovery of dihydroisoquinolinone derivatives as novel inhibitors of the p53-MDM2 interaction with a distinct binding mode." *Bioorg. Med. Chem. Lett.* 25: 3621-3625 (2015); Fry D. C. et al. "Deconstruction of a nutlin: dissecting the binding determinants of a potent protein-protein interaction inhibitor." *ACS Med Chem Lett* 4: 660-665 (2013); Ding Q. et al. "Discovery of RG7388 a Potent and Selective p53-MDM2 Inhibitor in Clinical Development." *J. Med. Chem.* 56: 5979-5983 (2013); Wang S. et al. "SAR405838: an optimized inhibitor of MDM2-p53 interaction that induces complete and durable tumor regression." *Cancer Res.* 74: 5855-5865 (2014); Rew Y. et al. "Discovery of AM-7209 a Potent and Selective 4-Amidobenzoic Acid Inhibitor of the MDM2-p53 Interaction." *J. Med. Chem.* 57: 10499-10511 (2014); Bogen S. L. et al. "Discovery of Novel 3 3-Disubstituted Piperidines as Orally Bioavailable Potent and Efficacious HDM2-p53 Inhibitors." *ACS Med. Chem. Lett.* 7: 324-329 (2016); and, Sun D. et al. "Discovery of AMG 232 a Potent Selective and Orally Bioavailable MDM2-p53 Inhibitor in Clinical Development." *J. Med. Chem.* 57: 1454-1472 (2014).

FIG. **2**AAAAA-**2**EEEEE present examples of PARP1, PARP2, and/or PARP3 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Iwashita A. et al. "Discovery of quinazolinone and quinoxaline derivatives as potent and selective poly(ADP-ribose) polymerase-1/2 inhibitors." *Febs Lett.* 579: 13 89-1393 (2005); the crystal structure PDB 2RCW (PARP complexed with A861695, Park C. H.); the crystal structure PDB 2RD6 (PARP complexed with A861696, Park C. H.); the crystal structure PDB 3GN7; Miyashiro J. et al. "Synthesis and SAR of novel tricyclic quinoxalinone inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1)" *Bioorg. Med. Chem. Lett.* 19: 4050-4054 (2009); Gandhi V. B. et al. "Discovery and SAR of substituted 3-oxoisoindoline-4-carboxamides as potent inhibitors of poly(ADP-ribose) polymerase (PARP) for the treatment of cancer." *Bioorg. Med. Chem. Lett.* 20: 1023-1026 (2010); Penning T. D. et al. "Optimization of phenyl-substituted benzimidazole carboxamide poly(ADP-ribose) polymerase inhibitors: identification of (S)-2-(2-fluoro-4-(pyrrolidin-2-yl)phenyl)-1H-benzimidazole-4-carboxamide (A-966492) a highly potent and efficacious inhibitor." *J. Med. Chem.* 53: 3142-3153 (2010); Ye N. et al. "Design, Synthesis, and Biological Evaluation of a Series of Benzo [de][1 7]naphthyridin-7 (8H)-ones Bearing a Functionalized

Longer Chain Appendage as Novel PARP1 Inhibitors." *J. Med. Chem.* 56: 2885-2903 (2013); Patel M. R. et al. "Discovery and Structure-Activity Relationship of Novel 2 3-Dihydrobenzofuran-7-carboxamide and 2 3-Dihydrobenzofuran-3(2H)-one-7-carboxamide Derivatives as Poly (ADP-ribose)polymerase-1 Inhibitors." *J. Med. Chem.* 57: 5579-5601 (2014); Thorsell A. G. et al. "Structural Basis for Potency and Promiscuity in Poly(ADP-ribose) Polymerase (PARP) and Tankyrase Inhibitors." *J. Med. Chem.* 60:1262-1271 (2012); the crystal structure PDB 4RV6 ("Human ARTD1 (PARP1) catalytic domain in complex with inhibitor Rucaparib", Karlberg T. et al.); Papeo G. M. E. et al. "Discovery of 2-[1-(4 4-Difluorocyclohexyl)Piperidin-4-Y1]-6-Fluoro-3-Oxo-2 3-Dihydro-1H-Isoindole-4-Carboxamide (Nms-P118): A Potent Orally Available and Highly Selective Parp-1 Inhibitor for Cancer Therapy." *J. Med. Chem.* 58: 6875 (2015); Kinoshita T. et al. "Inhibitor-induced structural change of the active site of human poly (ADP-ribose) polymerase." *Febs Lett.* 556: 43-46 (2004); and, Gangloff A. R. et al. "Discovery of novel benzo[b][1 4]oxazin-3(4H)-ones as poly(ADP-ribose)polymerase inhibitors." *Bioorg. Med. Chem. Lett.* 23: 4501-4505 (2013).

FIG. **2**FFFFF-**2**GGGGG present examples of PARP14 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**HHHHH presents examples of PARP15 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**IIIII presents examples of PDZ domain Targeting Ligands wherein R is the point at which the Linker(s) are attached.

FIG. **2**JJJJJ presents examples of Phospholipase A2 domain Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**KKKKK presents examples of Protein S100-A7 2WOS Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**LLLLL-**2**MMMMM present examples of Saposin-B Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**NNNNN-**2**OOOOO present examples of Sec7 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**PPPPP-**2**QQQQQ present examples of SH2 domain of pp60 Src Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**RRRRR presents examples of Tank1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**SSSSS presents examples of Ubc9 SUMO E2 ligase SF6D Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**TTTTT presents examples of Src Targenting Ligands, including AP23464, wherein R is the point at which the Linker is attached.

FIG. **2**UUUUU-**2**XXXXX present examples of Src-AS1 and/or Src AS2 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **2**YYYYY presents examples of JAK3 Targeting Ligands, including Tofacitinib, wherein R is the point at which the Linker is attached.

FIG. **2**ZZZZZ presents examples of ABL Targeting Ligands, including Tofacitinib and Ponatinib, wherein R is the point at which the Linker is attached.

FIG. **3**A-**3**B present examples of MEK1 Targeting Ligands, including PD318088, Trametinib and G-573, wherein R is the point at which the Linker is attached.

FIG. **3**C presents examples of KIT Targeting Ligands, including Regorafenib, wherein R is the point at which the Linker is attached.

FIG. **3**D-**3**E present examples of HIV Reverse Transcriptase Targeting Ligands, including Efavirenz, Tenofovir, Emtricitabine, Ritonavir, Raltegravir, and Atazanavir, wherein R is the point at which the Linker is attached.

FIG. **3**F-**3**G present examples of HIV Protease Targeting Ligands, including Ritonavir, Raltegravir, and Atazanavir, wherein R is the point at which the Linker is attached.

FIG. **3**H-**3**I present examples of KSR1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**J-**3**L present examples of CNNTB1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**M presents examples of BCL6 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**N-**3**O present examples of PAK1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**P-**3**R present examples of PAK4 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**S-**3**T present examples of TNIK Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**U presents examples of MEN1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**V-**3**W present examples of ERK1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**X presents examples of IDO1 Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**Y presents examples of CBP Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**Z-**3**SS present examples of MCL1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Tanaka Y. et al "Discovery of potent Mcl-1/Bcl-xL dual inhibitors by using a hybridization strategy based on structural analysis of target proteins." *J. Med. Chem.* 56: 9635-9645 (2013); Friberg A. et al. "Discovery of potent myeloid cell leukemia 1 (Mcl-1) inhibitors using fragment-based methods and structure-based design." *J. Med. Chem.* 56: 15-30 (2013); Petros A. M. et al "Fragment-based discovery of potent inhibitors of the anti-apoptotic MCL-1 protein." *Bioorg. Med. Chem. Lett.* 24: 1484-1488 (2014); Burke J. P. et al. "Discovery of tricyclic indoles that potently inhibit mcl-1 using fragment-based methods and structure-based design." *J. Med. Chem.* 58: 3794-3805 (2015); Pelz N. F. et al. "Discovery of 2-Indole-acylsulfonamide Myeloid Cell Leukemia 1 (Mcl-1) Inhibitors Using Fragment-Based Methods." *J. Med. Chem.* 59: 2054-2066 (2016); Clifton M. C. et al. "A Maltose-Binding Protein Fusion Construct Yields a Robust Crystallography Platform for MCL1." *Plos One* 10: e0125010-e0125010 (2015); Kotschy A et al. "The MCL1 inhibitor S63845 is tolerable and effective in diverse cancer models. *Nature* 538:477-482 (2016); EP 2886545 A1 titled "New thienopyrimidine derivatives a process for their preparation and pharmaceutical compositions containing them"; Jeffrey W. Johannes et al. "Structure Based Design of Non-Natural Peptidic Macrocyclic Mcl-1 Inhibitors" *ACS Med. Chem. Lett.* (2017); DOI: 10.1021/acsmedchemlett.6b00464; Bruncko M. et al. "Structure-Guided Design of a Series of MCL-1 Inhibitors with High Affinity and Selectivity." *J. Med. Chem.* 58: 2180-2194 (2015); Taekyu Lee et al. "Discovery and biological characterization of potent myeloid cell leukemia-1 inhibitors." *FEBS Letters* 591: 240-251 (2017); Chen L. et al. "Structure-Based Design of 3-Carboxy-Substituted 1 2 3 4-Tetra-

hydroquinolines as Inhibitors of Myeloid Cell Leukemia-1 (Mcl-1)." *Org. Biomol. Chem.* 14: 5505-5510 (2016); US 2016/0068545 titled "Tetrahydronaphthalene derivatives that inhibit mcl-1 protein"; WO 2016207217 A1 titled "Preparation of new bicyclic derivatives as pro-apoptotic agents"; Gizem Akgay et al. "Inhibition of Mcl-1 through covalent modification of a noncatalytic lysine side chain" *Nature Chemical Biology* 12: 931-936 (2016).

FIG. **3**TT presents examples of ASH1L Targeting Ligands wherein R is the point at which the Linker is attached. See for example, the crystal structure PDB 4YNM ("Human ASH1L SET domain in complex with S-adenosyl methionine (SAM)" Rogawski D. S. et al.)

FIG. **3**UU-**3**WW present examples of ATAD2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Chaikuad A. et al. "Structure-based approaches towards identification of fragments for the low-druggability ATAD2 bromodomain" *Med Chem Comm* 5: 1843-1848 (2014); Poncet-Montange G. et al. "Observed bromodomain flexibility reveals histone peptide- and small molecule ligand-compatible forms of ATAD2." *Biochem. J.* 466: 337-346 (2015); Harner M. J. et al. "Fragment-Based Screening of the Bromodomain of ATAD2." *J. Med. Chem.* 57: 9687-9692 (2014); Demont E. H. et al. "Fragment-Based Discovery of Low-Micromolar Atad2 Bromodomain Inhibitors." *J. Med. Chem.* 58: 5649 (2015); and, Bamborough P. et al. "Structure-Based Optimization of Naphthyridones into Potent Atad2 Bromodomain Inhibitors." *J Med. Chem.* 58: 6151 (2015).

FIG. **3**XX-**3**AAA present examples of BAZ2A and BAZ2B Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4CUU ("Human Baz2B in Complex with Fragment-6 N09645" Bradley A. et al.); the crystal structure PDB 5CUA ("Second Bromodomain of Bromodomain Adjacent to Zinc Finger Domain Protein 2B (BAZ2B) in complex with 1-Acetyl-4-(4-hydroxyphenyl)piperazine". Bradley A. et al.); Ferguson F. M. et al. "Targeting low-druggability bromodomains: fragment based screening and inhibitor design against the BAZ2B bromodomain." *J. Med. Chem.* 56: 10183-10187 (2013); Marchand J. R. et al. "Derivatives of 3-Amino-2-methylpyridine as BAZ2B Bromodomain Ligands: In Silico Discovery and in Crystallo Validation." *J. Med. Chem.* 59: 9919-9927 (2016); Drouin L. et al. "Structure Enabled Design of BAZ2-ICR A Chemical Probe Targeting the Bromodomains of BAZ2A and BAZ2B." *J. Med. Chem.* 58: 2553-2559 (2015); Chen P. et al. "Discovery and characterization of GSK2801 a selective chemical probe for the bromodomains BAZ2A and BAZ2B." *J. Med. Chem.* 59:1410-1424 (2016).

FIG. **3**BBB presents examples of BRD1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 5AME ("the Crystal Structure of the Bromodomain of Human Surface Epitope Engineered Brd1A in Complex with 3D Consortium Fragment 4-Acetyl-Piperazin-2-One Pearce", N. M. et al.); the crystal structure PDB 5AMF ("Crystal Structure of the Bromodomain of Human Surface Epitope Engineered Brd1A in Complex with 3D Consortium Fragment Ethyl 4 5 6 7-Tetrahydro-1H-Indazole-5-Carboxylate", Pearce N. M. et al.); the crystal structure PDB 5FG6 ("the Crystal structure of the bromodomain of human BRD1 (BRPF2) in complex with OF-1 chemical probe.", Tallant C. et al.); Filippakopoulos P. et al. "Histone recognition and large-scale structural analysis of the human bromodomain family." *Cell,* 149: 214-231 (2012).

FIG. **3**CCC-**3**EEE present examples of BRD2 Bromodomain 1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2ydw; the crystal structure PDB 2yek; the crystal structure PDB 4a9h; the crystal structure PDB 4a9f; the crystal structure PDB 4a9i; the crystal structure PDB 4a9m; the crystal structure PDB 4akn; the crystal structure PDB 4alg, and the crystal structure PDB 4uyf.

FIG. **3**FFF-**3**HHH present examples of BRD2 Bromodomain 2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 3oni; Filippakopoulos P. et al. "Selective Inhibition of BET Bromodomains." *Nature* 468: 1067-1073 (2010); the crystal structure PDB 4j1p; McLure K. G. et al. "RVX-208: an Inducer of ApoA-I in Humans is a BET Bromodomain Antagonist." *Plos One* 8: e83190-e83190 (2013); Baud M. G. et al. "Chemical biology. A bump-and-hole approach to engineer controlled selectivity of BET bromodomain chemical probes" *Science* 346: 638-641 (2014); Baud M. G. et al. "New Synthetic Routes to Triazolo-benzodiazepine Analogues: Expanding the Scope of the Bump-and-Hole Approach for Selective Bromo and Extra-Terminal (BET) Bromodomain Inhibition" *J. Med. Chem.* 59: 1492-1500 (2016); Gosmini R. et al. "The Discovery of I-Bet726 (Gsk1324726A) a Potent Tetrahydroquinoline Apoal Up-Regulator and Selective Bet Bromodomain Inhibitor" *J. Med. Chem.* 57: 8111 (2014); the crystal structure PDB 5EK9 ("Crystal structure of the second bromodomain of human BRD2 in complex with a hydroquinolinone inhibitor", Tallant C. et al); the crystal structure PDB 5BT5; the crystal structure PDB 5dfd; Baud M. G. et al. "New Synthetic Routes to Triazolo-benzodiazepine Analogues: Expanding the Scope of the Bump-and-Hole Approach for Selective Bromo and Extra-Terminal (BET) Bromodomain Inhibition" *J. Med. Chem.* 59: 1492-1500 (2016).

FIG. **3**III-**3**JJJ present examples of BRD4 Bromodomain 1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 5WUU and the crystal structure PDB 5F5Z.

FIG. **3**KKK-3LLL present examples of BRD4 Bromodomain 2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Chung C. W. et al. "Discovery and Characterization of Small Molecule Inhibitors of the Bet Family Bromodomains" *J. Med. Chem.* 54: 3827 (2011) and Ran X. et al. "Structure-Based Design of gamma-Carboline Analogues as Potent and Specific BET Bromodomain Inhibitors" *J. Med. Chem.* 58: 4927-4939 (2015).

FIG. **3**MMM presents examples of BRDT Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4flp and the crystal structure PDB 4kcx.

FIG. **3**NNN-**3**QQQ present examples of BRD9 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4nqn; the crystal structure PDB 4uit; the crystal structure PDB 4uiu; the crystal structure PDB 4uiv; the crystal structure PDB 4z6h; the crystal structure PDB 4z6i; the crystal structure PDB 5e9v; the

crystal structure PDB 5eul; the crystal structure PDB 5flh; and, the crystal structure PDB 5fp2.

FIG. **3**RRR presents examples of SMARCA4 PB1 and/or SMARCA2 Targeting Ligands wherein R is the point at which the Linker is attached, A is N or CH, and m is 0 1 2 3 4 5 6 7 or 8.

FIG. **3**SSS-**3**XXX present examples of additional Bromodomain Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Hewings et al. "3 5-Dimethylisoxazoles Act as Acetyl-lysine Bromodomain Ligands." *J.* Med. Chem. 54 6761-6770 (2011); Dawson et al. "Inhibition of BET Recruitment to Chromatin as an Effective Treatment for MLL-fusion Leukemia." *Nature,* 478, 529-533 (2011); US 2015/0256700; US 2015/0148342; WO 2015/074064; WO 2015/067770; WO 2015/022332; WO 2015/015318; and, WO 2015/011084.

FIG. **3**XXX-**3**YYY presents examples of PB1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 3mb4; the crystal structure PDB 4q0n; and, the crystal structure PDB 5fh6.

FIG. **3**ZZZ presents examples of SMARCA4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure 3uvd and the crystal structure 5dkd.

FIG. **3**AAAA presents examples of SMARCA2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure 5dkc and the crystal structure 5dkh.

FIG. **3**BBBB presents examples of TRIM24 (TIF1a) and/or BRPF1 Targeting Ligands wherein R is the point at which the Linker is attached and m is 0 1 2 3 4 5 6 7 or 8.

FIG. **3**CCCC presents examples of TRIM24 (TIF1a) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Palmer W. S. et al. "Structure-Guided Design of IACS-9571: a Selective High-Affinity Dual TRIM24-BRPF1 Bromodomain Inhibitor." *J. Med. Chem.* 59: 1440-1454 (2016).

FIG. **3**DDDD-**3**FFFF present examples of BRPF1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4uye; the crystal structure PDB 5c7n; the crystal structure PDB 5c87; the crystal structure PDB 5c89; the crystal structure PDB 5d7x; the crystal structure PDB 5dya; the crystal structure PDB Sepr; the crystal structure PDB 5eql; the crystal structure PDB Setb; the crystal structure PDB 5ev9; the crystal structure PDB Seva; the crystal structure PDB Sewv; the crystal structure PDB Seww; the crystal structure PDB 5ffy; the crystal structure PDB 5fg5; and, the crystal structure PDB 5g4r.

FIG. **3**GGGG presents examples of CECR2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Moustakim M. et al. *Med. Chem. Comm.* 7:2246-2264 (2016) and Crawford T. et al. *Journal of Med. Chem.* 59; 5391-5402 (2016).

FIG. **3**HHHH-**3**OOOO present examples of CREBBP Targeting Ligands wherein R is the point at which the Linker is attached, A is N or CH, and m is 0 1 2 3 4 5 6 7 or 8. For additional examples and related ligands, see, the crystal structure PDB 3p1d; the crystal structure PDB 3svh; the crystal structure PDB 4nr4; the crystal structure PDB 4nr5; the crystal structure PDB 4ts8; the crystal structure PDB 4nr6; the crystal structure PDB 4nr7; the crystal structure PDB 4nyw; the crystal structure PDB 4nyx; the crystal structure PDB 4tqn; the crystal structure PDB 5cgp; the crystal structure PDB 5dbm; the crystal structure PDB 5ep7; the crystal structure PDB 5i83; the crystal structure PDB 5i86; the crystal structure PDB 5i89; the crystal structure PDB 5i8g; the crystal structure PDB 5j0d; the crystal structure PDB 5ktu; the crystal structure PDB 5ktw; the crystal structure PDB 5ktx; the crystal structure PDB 5tb6.

FIG. **3**PPPP presents examples of EP300 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 5BT3.

FIG. **3**QQQQ presents examples of PCAF Targeting Ligands wherein R is the point at which the Linker is attached. See for example, M. Ghizzoni et al. *Bioorg. Med. Chem.* 18: 5826-5834 (2010).

FIG. **3**RRRR presents examples of PHIP Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, *Mol Cancer Ther.* 7(9): 2621-2632 (2008).

FIG. **3**SSSS presents examples of TAF1 and TAF1L Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Picaud S. et al. *Sci Adv* 2: e1600760-e1600760 (2016).

FIG. **3**TTTT presents examples of Histone Deacetylase 2 (HDAC2) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Lauffer B. E. *J. Biol. Chem.* 288: 26926-26943 (2013); *Wagner F. F. Bioorg. Med. Chem.* 24: 4008-4015 (2016); Bressi J. C. *Bioorg. Med. Chem. Lett.* 20: 3142-3145 (2010); and, Lauffer B. E. *J. Biol. Chem.* 288: 26926-26943 (2013).

FIG. **3**UUUU-**3**VVVV present examples of Histone Deacetylase 4 (HDAC4) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Burli R. W. *J. Med. Chem.* 56: 9934 (2013); Luckhurst C. A. *ACS Med. Chem. Lett.* 7: 34 (2016); *Bottomley M. J. J Biol. Chem.* 283: 26694-26704 (2008).

FIG. **3**WWWW presents examples of Histone Deaceytlase 6 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Harding R. J. (to be published); Hai Y. *Nat. Chem. Biol.* 12: 741-747, (2016); and, Miyake Y. *Nat. Chem. Biol.* 12: 748 (2016).

FIG. **3**XXXX and Fig. **3**YYYY present examples of Histone Deacetylase 7 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Lobera M. *Nat. Chem. Biol.* 9: 319 (2013) and Schuetz A. *J. Biol. Chem.* 283: 11355-11363 (2008).

FIG. **3**ZZZZ-**3**DDDDD present examples of Histone Deacetylase 8 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Whitehead L. Biol. *Med. Chem.* 19: 4626-4634 (2011); Tabackman A. A. *J. Struct. Biol.* 195: 373-378 (2016); Dowling D. P. *Biochemistry* 47, 13554-13563 (2008); Somoza J. R. *Biochemistry* 12, 1325-1334 (2004); Decroos C. *Biochemistry* 54: 2126-2135 (2015); Vannini A. *Proc. Natl Acad. Sci.* 101: 15064 (2004); Vannini A. *EMBO Rep.* 8: 879 (2007); the crystal structure PDB 5BWZ; Decroos A. *ACS Chem. Biol.* 9: 2157-2164 (2014); Somoza J. R. *Biochemistry* 12: 1325-1334 (2004); Decroos C. *Biochemistry* 54: 6501-6513 (2015); Decroos A. *ACS Chem. Biol.* 9: 2157-2164 (2014); and, Dowling D. P. *Biochemistry* 47: 13554-13563 (2008).

FIG. **3**EEEEE presents examples of Histone Acetyltransferase (KAT2B) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and

related ligands, see, Chaikuad A. *J. Med. Chem.* 59: 1648-1653 (2016); the crystal structure PDB 1ZS5; and, Zeng L. *J. Am. Chem. Soc.* 127: 2376-2377 (2005).

FIG. **3**FFFFF-**3**GGGGG present examples of Histone Acetyltransferase (KAT2A) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Ringel A. E. *Acta Crystallogr. D. Struct. Biol.* 72: 841-848 (2016).

FIG. **3**HHHHH presents examples of Histone Acetyltransferase Type B Catalytic Unit (HAT1) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2POW.

FIG. **3**IIIII presents examples of Cyclic AMP-dependent Transcription Factor (ATF2) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**JJJJJ presents examples of Histone Acetyltransferase (KAT5) Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**KKKKK-**3**MMMMM present examples of Lysine-specific histone demethylase 1A (KDM1A) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Mimasu S. *Biochemistry* 49: 6494-6503 (2010); Sartori L. *J. Med. Chem.* 60: 1673-1693 (2017); and, Vianello P. *J. Med. Chem.* 60: 1693-1715 (2017).

FIG. **3**NNNNN presents examples of HDAC6 Zn Finger Domain Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**OOOOO-**3**PPPPP present examples of general Lysine Methyltransferase Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **3**QQQQQ-**3**TTTTT present examples of DOT1L Targeting Ligands wherein R is the point at which the Linker is attached, A is N or CH, and m is 0 1 2 3 4 5 6 7 or 8. For additional examples and related ligands, see, the crystal structure PDB 5MVS ("DotlL in complex with adenosine and inhibitor CPD1" Be C. et al.); the crystal structure PDB 5MW4 ("Dot1L in complex inhibitor CPD7" Be C. et al.); the crystal structure PDB 5DRT ("Dot1L in complex inhibitor CPD2" Be C. et al.); Be C. et al. *ACS Med. Lett.* 8: 338-343 (2017); the crystal structure PDB 5JUW "(Dot1L in complex with SS148" Yu W. et al. Structural Genomics Consortium).

FIG. **3**UUUUU presents examples of EHMT1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 5TUZ ("EHMT1 in complex with inhibitor MS0124", Babault N. et al.).

FIG. **3**VVVVV presents examples of EHMT2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 5TUY ("EHMT2 in complex with inhibitor MS0124", Babault N. et al.); the PDB crystal structure 5TTF ("EHMT2 in complex with inhibitor MS012", Dong A. et al.); the PDB crystal structure 3RJW (Dong A. et al., Structural Genomics Consortium); the PDB crystal structure 3K5K; Liu F. et al. *J. Med. Chem.* 52: 7950-7953 (2009); and, the PDB crystal structure 4NVQ ("EHMT2 in complex with inhibitor A-366" Sweis R. F. et al.).

FIG. **3**WWWWW presents examples of SETD2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5LSY ("SETD2 in complex with cyproheptadine", Tisi D. et al.); Tisi D. et al. *ACS Chem. Biol.* 11: 3093-3105 (2016); the crystal structures PDB 5LSS, 5LSX, 5LSZ, 5LT6, 5LT7, and 5LT8; the PDB crystal structure 4FMU; and, Zheng W. et al. *J. Am. Chem. Soc.* 134: 18004-18014 (2012).

FIG. **3**XXXXX-**3**YYYYY present examples of SETD7 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5AYF ("SETD7 in complex with cyproheptadine." Niwa H. et al.); the PDB crystal structure 4JLG ("SETD7 in complex with (R)-PFI-2", Dong A. et al.); the PDB crystal structure 4JDS (Dong A. et. al Structural Genomics Consortium); the PDB crystal structure 4E47 (Walker J. R. et al. Structural Genomics Consortium; the PDB crystal structure 3VUZ ("SETD7 in complex with AAM-1." Niwa H. et al.); the PDB crystal structure 3VVO; and, Niwa H et al. *Acta Crystallogr. Sect.D* 69: 595-602 (2013).

FIG. **3**ZZZZZ presents examples of SETD8 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5TH7 ("SETD8 in complex with MS453", Yu W. et al.) and the PDB crystal structure 5T5G (Yu W et. al.; to be published).

FIG. **4**A-**4**B present examples of SETDB1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5KE2 ("SETDB1 in complex with inhibitor XST06472A", Iqbal A. et al.); the PDB crystal structure 5KE3 ("SETDB1 in complex with fragment MRT0181a", Iqbal A. et al.); the PDB crystal structure 5KH6 ("SETDB1 in complex with fragment methyl 3-(methylsulfonylamino)benzoate", Walker J. R. et al. Structural Genomics Consortium); and, the PDB crystal structure 5KCO ("SETDB1 in complex with [N]-(4-chlorophenyl)methanesulfonamide", Walker J. R. et al.)

FIG. **4**C-**4**P present examples of SMYD2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5KJK ("SMYD2 in complex with inhibitor AZ13450370", Cowen S. D. et al.); the PDB crystal structure 5KJM ("SMYD2 in complex with AZ931", Cowen S. D. et al.); the PDB crystal structure SKJN ("SMYD2 in complex with AZ506", Cowen S. D. et al.); the PDB crystal structure 5ARF ("SMYD2 in complex with N-[3-(4-chlorophenyl)-1-{N'-cyano-N-[3-(difluoromethoxy)phenyl] carbamimidoyl}-4 5-dihydro-1H-pyrazol-4-YL]-N-ethyl-2-hydroxyacetamide", Eggert E. et al.); the PDB crystal structure 5ARG ("SMYD2 in complex with BAY598", Eggert E. et al.); the PDB crystal structure 4YND ("SMYD2 in complex with A-893", Sweis R. F. et al.); the PDB crystal structure 4WUY ("SMYD2 in complex with LLY-507", Nguyen H. et al.); and, the PDB crystal structure 3S7B ("N-cyclohexyl-N-3-[2-(3 4-dichlorophenyl)ethyl]-N-(2-{[2-(5-hydroxy-3-oxo-3 4-dihydro-2H-1 4-benzoxazin-8-yl)ethyl] amino}ethyl)-beta-alaninamide", Ferguson A. D. et al.).

FIG. **4**Q-**4**R present examples of SMYD3 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure 5H17 ("SMYD3 in complex with 5'-{[(3S)-3-amino-3-carboxypropyl][3-(dimethylamino)propyl] amino}-5'-deoxyadenosine", Van Aller G. S. et al.); the crystal structure 5CCL ("SMYD3 in complex with oxindole compound", Mitchell L. H. et al.); and, the crystal structure 5CCM ("Crystal structure of SMYD3 with SAM and EPZ030456").

FIG. **4**S presents examples of SUV4-20H1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see,

the PDB crystal structure 5CPR ("SUV4-20H1 in complex with inhibitor A-196", Bromberg K. D. et al.).

FIG. **4**T-**4**AA present examples of Wild Type Androgen Receptor Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structures 5T8E and 5T8J ("Androgen Receptor in complex with 4-(pyrrolidin-1-yl) benzonitrile derivatives", Asano M. et al.); Asano M. et al. *Bioorg. Med. Chem.* Lett. 27: 1897-1901 (2017); the PDB crystal structure 5JJM ("Androgen Receptor", Nadal M. et al.); the PDB crystal structure 5CJ6 ("Androgen Receptor in complex with 2-Chloro-4-[[(1R 2R)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile derivatives", Saeed A. et al.); the PDB crystal structure 4QL8 ("Androgen Receptor in complex with 3-alkoxy-pyrrolo[1 2-b]pyrazolines derivatives", Ullrich T. et al.); the PDB crystal structure 4HLW ("Androgen Receptor Binding Function 3 (BF3) Site of the Human Androgen Receptor through Virtual Screening", Munuganti R. S. et al.); the PDB crystal structure 3V49 ("Androgen Receptor lbd with activator peptide and sarm inhibitor 1", Nique F. et al.); Nique F. et al. *J. Med. Chem.* 55: 8225-8235 (2012); the PDB crystal structure 2YHD ("Androgen Receptor in complex with AF2 small molecule inhibitor", Axerio-Cilies P. et al.); the PDB crystal structure 3RLJ ("Androgen Receptor ligand binding domain in complex with SARM S-22", Bohl C. E. et al.); Bohl C. E. et al. *J. Med. Chem.* 54: 3973-3976 (2011); the PDB crystal structure 3B5R ("Androgen Receptor ligand binding domain in complex with SARM C-31", Bohl C. E. et al.); Bohl C. E. et al. *Bioorg. Med. Chem. Lett.* 18: 5567-5570 (2008); the PDB crystal structure 2PIP ("Androgen Receptor ligand binding domain in complex with small molecule", Estebanez-Perpina E. et al.); Estebanez-Perpina. E. *Proc. Natl. Acad. Sci.* 104:16074-16079 (2007); the PDB crystal structure 2PNU ("Androgen Receptor ligand binding domain in complex with EM5744", Cantin L. et al.); and, the PDB crystal structure 2HVC ("Androgen Receptor ligand binding domain in complex with LGD2226", Wang F. et al.). For additional related ligands, see, Matias P. M. et al. "Structural Basis for the Glucocorticoid Response in a Mutant Human Androgen Receptor (Ar(Ccr)) Derived from an Androgen-Independent Prostate Cancer." *J. Med. Chem.* 45: 1439 (2002); Sack J. S. et al. "Crystallographic structures of the ligand-binding domains of the androgen receptor and its T877A mutant complexed with the natural agonist dihydrotestosterone." *Proc. Natl. Acad. Sci.* 98: 4904-4909 (2001); He B. et al. "Structural basis for androgen receptor interdomain and coactivator interactions suggests a transition in nuclear receptor activation function dominance." *Mol. Cell* 16: 425-438 (2004); Pereira de Jesus-Tran K. "Comparison of crystal structures of human androgen receptor ligand-binding domain complexed with various agonists reveals molecular determinants responsible for binding affinity." *Protein Sci.* 15: 987-999 (2006); Bohl C. E. et al. "Structural Basis for Accommodation of Nonsteroidal Ligands in the Androgen Receptor." *Mol Pharmacol.* 63(1): 211-23 (2003); Sun C. et al. "Discovery of potent orally-active and muscle-selective androgen receptor modulators based on an N-aryl-hydroxybicyclohydantoin scaffold." *J. Med.* Chem. 49: 7596-7599 (2006); Nirschl A. A. et al. "N-aryl-oxazolidin-2-imine muscle selective androgen receptor modulators enhance potency through pharmacophore reorientation." *J Med. Chem.* 52: 2794-2798 (2009); Bohl C. E. et al. "Effect of B-ring substitution pattern on binding mode of propionamide selective androgen receptor modulators." *Bioorg. Med. Chem. Lett.* 18: 5567-5570 (2008); Ullrich T. et al. "3-alkoxy-pyrrolo[1 2-b]pyrazolines as selective androgen receptor modulators with ideal physicochemical properties for transdermal administration." J. *Med. Chem.* 57: 7396-7411 (2014); Saeed A. et al. "2-Chloro-4-[[(1R 2R)-2-hydroxy-2-methyl-cyclopentyl] amino]-3-methyl-benzonitrile: A Transdermal Selective Androgen Receptor Modulator (SARM) for Muscle Atrophy." *J. Med. Chem.* 59: 750-755 (2016); Nique et al. "Discovery of diarylhydantoins as new selective androgen receptor modulators." *J. Med. Chem.* 55: 8225-8235 (2012); and, Michael E. Jung et al. "Structure-Activity Relationship for Thiohydantoin Androgen Receptor Antagonists for Castration-Resistant Prostate Cancer (CRPC)." *J Med. Chem.* 53: 2779-2796 (2010).

FIG. **4**BB presents examples of Mutant T877A Androgen Receptor Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4OGH ('Androgen Receptor T877A-AR-LBD", Hsu C. L. et al.) and the PDB crystal structure 2OZ7 ("Androgen Receptor T877A-AR-LBD", Bohl C. E. et al.).

FIG. **4**CC presents examples of Mutant W741L Androgen Receptor Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4OJB ("Androgen Receptor T877A-AR-LBD", Hsu C. L. et al.).

FIG. **4**DD-4EE presents examples of Estrogen and/or Androgen Targeting Ligands wherein R is the point at which the Linker is attached.

FIG. **5**A presents examples of Afatinib, a Targeting Ligands for the EGFR and ErbB2/4 receptors. R is the point at which the Linker is attached.

FIG. **5**B presents examples of Axitinib, a Targeting Ligands for the VEGFR1/2/3, PDGFRP3, and Kit receptors. R is the point at which the Linker is attached.

FIG. **5**C-**5**D present examples of Bosutinib, a Targeting Ligands for the BCR-Abl, Src, Lyn and Hck receptors. R is the point at which the Linker is attached.

FIG. **5**E presents examples of Cabozantinib, a Targeting Ligands for the RET, c-Met, VEGFR1/2/3, Kit, TrkB, Flt3, Axl, and Tie 2 receptors. R is the point at which the Linker is attached.

FIG. **5**F presents examples of Ceritinib, a Targeting Ligands for the ALK, IGF-1R, InsR, and ROS1 receptors. R is the point at which the Linker is attached.

FIG. **5**G presents examples of Crizotinib, a Targeting Ligands for the ALK, c-Met, HGFR, ROS1, and MST1R receptors. R is the point at which the Linker is attached.

FIG. **5**H presents examples of Dabrafenib, a Targeting Ligands for the B-Raf receptor. R is the point at which the Linker is attached.

FIG. **5**I presents examples of Dasatinib, a Targeting Ligands for the BCR-Abl, Src, Lck, Lyn, Yes, Fyn, Kit, EphA2, and PDGFRP3 receptors. R is the point at which the Linker is attached.

FIG. **5**J presents examples of Erlotinib, a Targeting Ligands for the EGFR receptor. R is the point at which the Linker is attached.

FIG. **5**K-**5**M presents examples of Everolimus, a Targeting Ligands for the HER2 breast cancer receptor, the PNET receptor, the RCC receptors, the RAML receptor, and the SEGA receptor. R is the point at which the Linker is attached.

FIG. **5**N presents examples of Gefitinib, a Targeting Ligands for the EGFR and PDGFR receptors. R is the point at which the Linker is attached.

FIG. **5**O presents examples of Ibrutinib, a Targeting Ligands for the BTK receptor. R is the point at which the Linker is attached.

FIG. **5**P-**5**Q present examples of Imatinib, a Targeting Ligands for the BCR-Abl, Kit, and PDGFR receptors. R is the point at which the Linker is attached.

FIG. **5**R-**5**S present examples of Lapatinib, a Targeting Ligands for the EGFR and ErbB2 receptors. R is the point at which the Linker is attached.

FIG. **5**T presents examples of Lenvatinib, a Targeting Ligands for the VEGFR1/2/3, FGFR1/2/3/4, PDGFRα, Kit, and RET receptors. R is the point at which the Linker is attached.

FIG. **5**U-**5**V a present examples of Nilotinib, a Targeting Ligands for the BCR-Abl, PDGRF, and DDR1 receptors. R is the point at which the Linker is attached.

FIG. **5**W-**5**X present examples of Nintedanib, a Targeting Ligands for the FGFR1/2/3, Flt3, Lck, PDGFRα/β, and VEGFR1/2/3 receptors. R is the point at which the Linker is attached.

FIG. **5**Y-**5**Z present examples of Palbociclib, a Targeting Ligands for the CDK4/6 receptor. R is the point at which the Linker is attached.

FIG. **5**AA presents examples of Pazopanib, a Targeting Ligands for the VEGFR1/2/3, PDGFRα/(3, FGFR1/3, Kit, Lck, Fms, and Itk receptors. R is the point at which the Linker is attached.

FIG. **5**BB-**5**CC present examples of Ponatinib, a Targeting Ligands for the BCR-Abl, T315I VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, and Flt3 receptors. R is the point at which the Linker is attached.

FIG. **5**DD presents examples of Regorafenib, a Targeting Ligands for the VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/(3, RET, FGFR1/2, Tie2, and Eph2A. R is the point at which the Linker is attached.

FIG. **5**EE presents examples of Ruxolitinib, a Targeting Ligands for the JAK1/2 receptors. R is the point at which the Linker is attached.

FIG. **5**FF-**5**GG present examples of Sirolimus, a Targeting Ligands for the FKBP12/mTOR receptors. R is the point at which the Linker is attached.

FIG. **5**HH presents examples of Sorafenib, a Targeting Ligands for the B-Raf, CDK8, Kit, Flt3, RET, VEGFR1/2/3, and PDGFR receptors. R is the point at which the Linker is attached.

FIG. **5**II-**5**JJ present examples of Sunitinib, a Targeting Ligands for PDGFRα/P3, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET. R is the point at which the Linker is attached.

FIG. **5**KK-**5**LL present examples of Temsirolimus, a Targeting Ligands FKBP12/mTOR. R is the point at which the Linker is attached.

FIG. **5**MM presents examples of Tofacitinib, a Targeting Ligands for JAK3 receptors. R is the point at which the Linker is attached.

FIG. **5**NN presents examples of Trametinib, a Targeting Ligands for the MEK1/2 receptors. R is the point at which the Linker is attached.

FIG. **5**OO-**5**PP presents examples of Vandetanib, a Targeting Ligands for the EGFR, VEGFR, RET, Tie2, Brk, and EphR. R is the point at which the Linker is attached.

FIG. **5**QQ presents examples of Vemurafenib, a Targeting Ligands for the A/B/C-Raf, KSR1, and B-Raf (V600E) receptors. R is the point at which the Linker is attached.

FIG. **5**RR presents examples of Idelasib, a Targeting Ligands for the PI3Ka receptor. R is the point at which the Linker is attached.

FIG. **5**SS presents examples of Buparlisib, a Targeting Ligands for the PI3Ka receptor. R is the point at which the Linker is attached.

FIG. **5**TT presents examples of Taselisib, a Targeting Ligands for the PI3Ka receptor. R is the point at which the Linker is attached.

FIG. **5**UU presents examples of Copanlisib, a Targeting Ligands for the PI3Ka. R is the point at which the Linker is attached.

FIG. **5**VV presents examples of Alpelisib, a Targeting Ligands for the PI3Ka. R is the point at which the Linker is attached.

FIG. **5**WW presents examples of Niclosamide, a Targeting Ligands for the CNNTB1. R is the point at which the Linker is attached.

FIG. **6**A-**6**B present examples of the BRD4 Bromodomains of PCAF and GCN5 receptors 1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5tpx ("Discovery of a PCAF Bromodomain Chemical Probe"); Moustakim, M., et al. *Angew. Chem. Int. Ed. Engl.* 56: 827 (2017); the PDB crystal structure 5mlj ("Discovery of a Potent, Cell Penetrant, and Selective p300/CBP-Associated Factor (PCAF)/General Control Nonderepressible 5 (GCN5) Bromodomain Chemical Probe"); and, Humphreys, P. G. et al. *J. Med. Chem.* 60: 695 (2017).

FIG. **6**C-**6**D present examples of G9a (EHMT2) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 3k5k; ("Discovery of a 2,4-diamino-7-aminoalkoxyquinazoline as a potent and selective inhibitor of histone lysine methyltransferase G9a"); Liu, F. et al. J. Med. Chem. 52: 7950 (2009); the PDB crystal structure 3rjw ("A chemical probe selectively inhibits G9a and GLP methyltransferase activity in cells"); Vedadi, M. et al. Nat. Chem. Biol. 7: 566 (2011); the PDB crystal structure 4nvq ("Discovery and development of potent and selective inhibitors of histone methyltransferase g9a"); and, Sweis, R. F. et al. *ACSMed Chem Lett* 5: 205 (2014).

FIG. **6**E-**6**G present examples of EZH2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 5ij8 ("Polycomb repressive complex 2 structure with inhibitor reveals a mechanism of activation and drug resistance"); Broun, A. et al. *Nat Commun* 7: 11384 (2016); the PDB crystal structure 5ls6 ("Identification of (R)—N-((4-Methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl) methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (CPI-1205), a Potent and Selective Inhibitor of Histone Methyltransferase EZH2, Suitable for Phase I Clinical Trials for B-Cell Lymphomas"); Vaswani, R. G. et al. *J Med. Chem.* 59: 9928 (2016); and, the PDB crystal structures 5ij8 and 5ls6.

FIG. **6**H-**6**I present examples of EED Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structures 5h15 and 5h19 ("Discovery and Molecular Basis of a Diverse Set of Polycomb Repressive Complex 2 Inhibitors Recognition by EED"); Li, L. et al. *PLoS ONE* 12: e0169855 (2017); and, the PDB crystal structure 5h19.

FIG. **6**J presents examples of KMT5A (SETD8) Targeting Ligands wherein R is the point at which the Linker is attached. See for example, the PDB crystal structure 5t5g.

FIG. **6**K-**6**L present examples of DOT1L Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4eki ("Conformational adaptation

drives potent, selective and durable inhibition of the human protein methyltransferase DOT1L"); Basavapathruni, A. et al. *Chem. Biol. DrugDes.* 80: 971 (2012); the PDB crystal structure 4hra ("Potent inhibition of DOT1L as treatment of MLL-fusion leukemia"); Daigle, S. R. et al. *Blood* 122: 1017 (2013); the PDB crystal structure 5dry ("Discovery of Novel Dot1L Inhibitors through a Structure-Based Fragmentation Approach") Chen, C. et al. *ACSMed. Chem. Lett.* 7: 735 (2016); the PDB crystal structure 5dt2 ("Discovery of Novel Dot1L Inhibitors through a Structure-Based Fragmentation Approach"); and, Chen, C. et al. *ACSMed. Chem. Lett.* 7: 735 (2016).

FIG. **6**M-**6**N present examples of PRMT3 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 3smq ("An allosteric inhibitor of protein arginine methyltransferase 3"); Siarheyeva, A. et al. *Structure* 20: 1425 (2012); PDB crystal structure 4ryl ("A Potent, Selective and Cell-Active Allosteric Inhibitor of Protein Arginine Methyltransferase 3 (PRMT3)"); and Kaniskan, H. U. et al. *Angew. Chem. Int. Ed. Engl.* 54: 5166 (2015).

FIG. **6**O presents examples of CARM 1 (PRMT4) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structures 2y1x and 2y1w and related ligands described in "Structural Basis for Carml Inhibition by Indole and Pyrazole Inhibitors." Sack, J. S. et al. *Biochem. J.* 436: 331 (2011).

FIG. **6**P presents examples of PRMT5 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4×61 and related ligands described in "A selective inhibitor of PRMT5 with in vivo and in vitro potency in MCL models". Chan-Penebre, E. *Nat. Chem. Biol.* 11: 432 (2015).

FIG. **6**Q presents examples of PRMT6 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4y30 and related ligands described in "Aryl Pyrazoles as Potent Inhibitors of Arginine Methyltransferases: Identification of the First PRMT6 Tool Compound". Mitchell, L. H. et al. *ACS Med. Chem. Lett.* 6: 655 (2015).

FIG. **6**R presents examples of LSD1 (KDM1A) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 51gu and related ligands described in "Thieno[3,2-b]pyrrole-5-carboxamides as New Reversible Inhibitors of Histone Lysine Demethylase KDM1A/LSD1. Part 2: Structure-Based Drug Design and Structure-Activity Relationship". Vianello, P. et al. *J. Med. Chem.* 60: 1693 (2017).

FIG. **6**S-**6**T present examples of KDM4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 3rvh; the PDB crystal structure 5a7p and related ligands described in "Docking and Linking of Fragments to Discover Jumonji Histone Demethylase Inhibitors." Korczynska, M., et al. *J. Med. Chem.* 59: 1580 (2016); and, the PDB crystal structure 3f3c and related ligands described in "8-Substituted Pyrido[3,4-d]pyrimidin-4(3H)-one Derivatives As Potent, Cell Permeable, KDM4 (JMJD2) and KDM5 (JARID1) Histone Lysine Demethylase Inhibitors." Bavetsias, V. et al. J. *Med. Chem.* 59: 1388 (2016).

FIG. **6**U presents examples of KDM5 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 3fun and related ligands described in "Structural Analysis of Human Kdm5B Guides Histone Demethylase Inhibitor Development". Johansson, C. et al. *Nat. Chem. Biol.* 12: 539 (2016) and the PDB crystal structure 5ceh and related ligands described in "An inhibitor of KDM5 demethylases reduces survival of drug-tolerant cancer cells". Vinogradova, M. et al. *Nat. Chem. Biol.* 12: 531 (2016).

FIG. **6**V-**6**W present examples of KDM6 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4ask and related ligands described in "A Selective Jumonji H3K27 Demethylase Inhibitor Modulates the Proinflammatory Macrophage Response". Kruidenier, L. et al. *Nature* 488: 404 (2012).

FIG. **6**X presents examples of L3MBTL3 targeting ligands wherein R is the point at which the Linker is attached. See for example, the PDB crystal structure 4fl6.

FIG. **6**Y presents examples of Menin Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 4x5y and related ligands described in "Pharmacologic Inhibition of the Menin-MLL Interaction Blocks Progression of MLL Leukemia In Vivo" Borkin, D. et al. *Cancer Cell* 27: 589 (2015) and the PDB crystal structure 4og8 and related ligands described in "High-Affinity Small-Molecule Inhibitors of the Menin-Mixed Lineage Leukemia (MLL) Interaction Closely Mimic a Natural Protein-Protein Interaction" He, S. et al. *J. Med. Chem.* 57: 1543 (2014).

FIG. **6**Z-**6**AA present examples of HDAC6 Targeting Ligands wherein R is the point at which the Linker is attached. See for example, the PDB crystal structures 5kh3 and 5eei.

FIG. **6**BB presents examples of HDAC7 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 3c10 and related ligands described in "Human HDAC7 harbors a class IIa histone deacetylase-specific zinc binding motif and cryptic deacetylase activity." Schuetz, A. et al. *J. Biol. Chem.* 283: 11355 (2008) and the PDB crystal structure PDB 3zns and related ligands described in "Selective Class Iia Histone Deacetylase Inhibition Via a Non-Chelating Zinc Binding Group". Lobera, M. et al. *Nat. Chem. Biol.* 9: 319 (2013).

FIG. **7**A-**7**C present examples of Protein Tyrosine Phosphatase, Non-Receptor Type 1, PTP1B Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the PDB crystal structure 1bzj described in "Structural basis for inhibition of the protein tyrosine phosphatase 1B by phosphotyrosine peptide mimetics" Groves, M. R. et al. *Biochemistry* 37: 17773-17783 (1998); the PDB crystal structure 3cwe described in "Discovery of [(3-bromo-7-cyano-2-naphthyl)(difluoro)methyl]phosphonic acid, a potent and orally active small molecule PTP1B inhibitor". Han Y, *Bioorg Med Chem Lett.* 18:3200-5 (2008); the PDB crystal structures 2azr and 2b07 described in "Bicyclic and tricyclic thiophenes as protein tyrosine phosphatase 1B inhibitors." Moretto, A. F. et al. *Bioorg. Med. Chem.* 14: 2162-2177 (2006); the PDB crystal structures PDB 2bgd, 2bge, 2cm7, 2cm8, 2cma, 2cmb, 2cmc described in ""Structure-Based Design of Protein Tyrosine Phosphatase-1B Inhibitors". Black, E. et al. *Bioorg. Med. Chem. Lett.* 15: 2503 (2005) and "Structural Basis for Inhibition of Protein-Tyrosine Phosphatase 1B by Isothiazolidinone Heterocyclic Phosphonate Mimetics." Ala, P. J. et al. *J. Biol. Chem.* 281: 32784 (2006); the PDB crystal structures 2f6t and 2f6w described in "1,2,3,4-Tet-

rahydroisoquinolinyl sulfamic acids as phosphatase PTP1B inhibitors". Klopfenstein, S. R. et al. *Bioorg. Med. Chem. Lett.* 16: 1574-1578 (2006); the PDB crystal structures 2h4g, 2h4k, 2hbl described in ""Monocyclic thiophenes as protein tyrosine phosphatase lB inhibitors: Capturing interactions with Asp48." Wan, Z. K. et al. *Bioorg. Med. Chem. Lett.* 16: 4941-4945 (2006); the PDB crystal structures 2zn7 described in "Structure-based optimization of protein tyrosine phosphatase-1 B inhibitors: capturing interactions with arginine 24". Wan, Z. K. et al. *Chem Med Chem.* 3:1525-9 (2008); the PDB crystal structure 2nt7, 2nta described in "Probing acid replacements of thiophene PTP1B inhibitors." Wan, Z. K. et al. Bioorg. Med. Chem. Lett. 17: 2913-2920 (2007); and, WO 2008148744 A1 assigned to Novartis AG titled "Thiadiazole derivatives as antidiabetic agents". See also, the PDB crystal structures 1c84, 1c84, 1c85, 1c86, 1c88, 118g and described in ""2-(oxalylamino)-benzoic acid is a general, competitive inhibitor of protein-tyrosine phosphatases". Andersen, H. S. et al. *J. Biol. Chem.* 275: 7101-7108 (2000); "Structure-based design of a low molecular weight, nonphosphorus, nonpeptide, and highly selective inhibitor of protein-tyrosine phosphatase 1B." Iversen, L. F. et al. *J Biol. Chem.* 275: 10300-10307 (2000); and, "Steric hindrance as a basis for structure-based design of selective inhibitors of protein-tyrosine phosphatases". Iversen, L. F. et al. *Biochemistry* 40: 14812-14820 (2001).

FIG. **7**D presents examples of Tyrosine-protein phosphatase non-receptor type 11, SHP2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 4pvg and 305x and described in "Salicylic acid based small molecule inhibitor for the oncogenic Src homology-2 domain containing protein tyrosine phosphatase-2 (SHP2)." Zhang, X. et al. *J. Med. Chem.* 53: 2482-2493 (2010); and, the crystal structure PDB 5ehr and related ligands described in "Allosteric Inhibition of SHP2: Identification of a Potent, Selective, and Orally Efficacious Phosphatase Inhibitor." Garcia Fortanet, J. et al. *J. Med. Chem.* 59: 7773-7782 (2016). Also, see the crystal structure PDB 5ehr described in "Allosteric Inhibition of SHP2: Identification of a Potent, Selective, and Orally Efficacious Phosphatase Inhibitor." Garcia Fortanet, J. et al. *J. Med. Chem.* 59: 7773-7782 (2016) and "Allosteric inhibition of SHP2 phosphatase inhibits cancers driven by receptor tyrosine kinases." Chen, Y. P. et al. *Nature* 535: 148-152 (2016).

FIG. **7**E presents examples of Tyrosine-protein phosphatase non-receptor type 22 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4j51 described in "A Potent and Selective Small-Molecule Inhibitor for the Lymphoid-Specific Tyrosine Phosphatase (LYP), a Target Associated with Autoimmune Diseases." He, Y. et al. *J Med. Chem.* 56: 4990-5008 (2013).

FIG. **7**F presents examples of Scavenger mRNA-decapping enzyme DcpS Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 3b17, 3b19, 3bla, 4qde, 4qdv, 4qeb and related ligands described in "DcpS as a therapeutic target for spinal muscular atrophy." Singh, J. et al. *ACS Chem. Biol.* 3: 711-722 (2008).

FIG. **8**A-**8**S present examples of BRD4 Bromodomain 1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 3u5k and 3u51 and related ligands in Filippakopoulos, P. et al. "Benzodiazepines and benzotriazepines as protein interaction inhibitors targeting bromodomains of the BET family", *Bioorg. Med. Chem.* 20: 1878-1886 (2012); the crystal structure PDB 3u51; the crystal structure PDB 3zyu and related ligands described in Dawson, M. A. et al. "Inhibition of Bet Recruitment to Chromatin as an Effective Treatment for Mll-Fusion Leukaemia." *Nature* 478: 529 (2011); the crystal structure PDB 4bwl and related ligands described in Mirguet, O. et al. "Naphthyridines as Novel Bet Family Bromodomain Inhibitors." *Chemmedchem* 9: 589 (2014); the crystal structure PDB 4cfl and related ligands described in Dittmann, A. et al. "The Commonly Used Pi3-Kinase Probe Ly294002 is an Inhibitor of Bet Bromodomains" *ACS Chem. Biol.* 9: 495 (2014); the crystal structure PDB 4e96 and related ligands described in Fish, P. V. et al. "Identification of a chemical probe for bromo and extra C-terminal bromodomain inhibition through optimization of a fragment-derived hit." *J. Med. Chem.* 55: 9831-9837 (2012); the crystal structure PDB 4clb and related ligands described in Atkinson, S. J. et al. "The Structure Based Design of Dual Hdac/Bet Inhibitors as Novel Epigenetic Probes." *Medchemcomm* 5: 342 (2014); the crystal structure PDB 4f3i and related ligands described in Zhang, G. et al. "Down-regulation of NF-{kappa}B Transcriptional Activity in HIV-associated Kidney Disease by BRD4 Inhibition." *J. Biol. Chem.* 287: 28840-28851 (2012); the crystal structure PDB 4hxl and related ligands described in Zhao, L. "Fragment-Based Drug Discovery of 2-Thiazolidinones as Inhibitors of the Histone Reader BRD4 Bromodomain." *J. Med. Chem.* 56: 3833-3851 (2013); the crystal structure PDB 4hxs and related ligands described in Zhao, L. et al. "Fragment-Based Drug Discovery of 2-Thiazolidinones as Inhibitors of the Histone Reader BRD4 Bromodomain." *J. Med. Chem.* 56: 3833-3851 (2013); the crystal structure PDB 41rg and related ligands described in Gehling, V. S. et al. "Discovery, Design, and Optimization of Isoxazole Azepine BET Inhibitors." *ACS Med Chem Lett* 4: 835-840 (2013); the crystal structure PDB 4mep and related ligands described in Vidler, L. R. "Discovery of Novel Small-Molecule Inhibitors of BRD4 Using Structure-Based Virtual Screening." et al. *J. Med. Chem.* 56: 8073-8088 (2013); the crystal structures PDB 4nr8 and PDB 4c77 and related ligands described in Ember, S. W. et al. "Acetyl-lysine Binding Site of Bromodomain-Containing Protein 4 (BRD4) Interacts with Diverse Kinase Inhibitors". *ACS Chem. Biol.* 9: 1160-1171 (2014); the crystal structure PDB 4o7a and related ligands described in Ember, S. W. et al. "Acetyl-lysine Binding Site of Bromodomain-Containing Protein 4 (BRD4) Interacts with Diverse Kinase Inhibitors." *ACS Chem. Biol.* 9: 1160-1171 (2014); the crystal structure PDB 407b and related ligands described in "Acetyl-lysine Binding Site of Bromodomain-Containing Protein 4 (BRD4) Interacts with Diverse Kinase Inhibitors." Ember, S. W. et al. (2014) *ACS Chem. Biol.* 9: 1160-1171; the crystal structure PDB 4o7c and related ligands described in Ember, S. W. et al. "Acetyl-lysine Binding Site of Bromodomain-Containing Protein 4 (BRD4) Interacts with Diverse Kinase Inhibitors". *ACS Chem. Biol.* 9: 1160-1171 (2014); the crystal structure PDB 4gpj; the crystal structure PDB 4uix and related ligands described in Theodoulou, N. H. et al. "The Discovery of I-Brd9, a Selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition". *J. Med. Chem.* 59: 1425 (2016); the crystal structure PDB 4uiz and related ligands described in Theodoulou, N. H., et al. "The Discovery of I-Brd9, a Selective Cell Active Chemical Probe for Bromodomain Containing Protein 9 Inhibition". *J. Med. Chem.* 59: 1425 (2016); the crystal structure PDB 4wiv and related ligands described in McKeown, M. R. et al. "Biased multicomponent reactions to develop novel bromodomain inhibitors." *J. Med. Chem.* 57: 9019-9027 (2014); the crystal

structure PDB 4x2i and related ligands described in Taylor, A. M. et al. "Discovery of Benzotriazolo[4,3-d][1,4]diazepines as Orally Active Inhibitors of BET Bromodomains." *ACS Med. Chem. Lett.* 7: 145-150 (2016); the crystal structure PDB 4yh3; And related ligands described in Duffy, B. C. "Discovery of a new chemical series of BRD4(1) inhibitors using protein-ligand docking and structure-guided design." *Bioorg. Med. Chem. Lett.* 25: 2818-2823 (2015); the crystal structure PDB 4yh4 and related ligands described in Duffy, B. C. "Discovery of a new chemical series of BRD4(1) inhibitors using protein-ligand docking and structure-guided design." *Bioorg. Med. Chem. Lett.* 25: 2818-2823 (2015); the crystal structure PDB 4zlq and related ligands described in Taylor, A. M. "Discovery of Benzotriazolo[4,3-d][1,4]diazepines as Orally Active Inhibitors of BET Bromodomains." *ACSMed. Chem. Lett.* 7: 145-150 (2016); the crystal structure PDB 4zwl; the crystal structure PDB 5a5s and related ligands described in Demont, E. H. "Fragment-Based Discovery of Low-Micromolar Atad2 Bromodomain Inhibitors. *J. Med. Chem.* 58: 5649 (2015); the crystal structure PDB 5a85 and related ligands described in Bamborough, P. "Structure-Based Optimization of Naphthyridones Into Potent Atad2 Bromodomain Inhibitors" *J. Med. Chem.* 58: 6151 (2015); the crystal structure PDB 5acy and related ligands described in Sullivan, J. M. "Autism-Like Syndrome is Induced by Pharmacological Suppression of Bet Proteins in Young Mice." *J Exp. Med.* 212: 1771 (2015); the crystal structure PDB 5ad2 and related ligands described in Waring, M. J. et al. "Potent and Selective Bivalent Inhibitors of Bet Bromodomains". *Nat. Chem. Biol.* 12: 1097 (2016); the crystal structure PDB 5cfw and related ligands described in Chekler, E. L. et al. "Transcriptional Profiling of a Selective CREB Binding Protein Bromodomain Inhibitor Highlights Therapeutic Opportunities." *Chem. Biol.* 22: 1588-1596 (2015); the crystal structure PDB 5cqt and related ligands described in Xue, X. et al. "Discovery of Benzo[cd]indol-2(1H)-ones as Potent and Specific BET Bromodomain Inhibitors: Structure-Based Virtual Screening, Optimization, and Biological Evaluation". *J. Med. Chem.* 59: 1565-1579 (2016); the crystal structure PDB 5d3r and related ligands described in Hugle, M. et al. "4-Acyl Pyrrole Derivatives Yield Novel Vectors for Designing Inhibitors of the Acetyl-Lysine Recognition Site of BRD4(1)". *J. Med. Chem.* 59: 1518-1530 (2016); the crystal structure PDB 5dlx and related ligands described in Milhas, S. et al. "Protein-Protein Interaction Inhibition (2P2I)-Oriented Chemical Library Accelerates Hit Discovery." (2016) *ACS Chem. Biol.* 11: 2140-2148; the crystal structure PDB 5dlz and related ligands described in Milhas, S. et al. "Protein-Protein Interaction Inhibition (2P2I)-Oriented Chemical Library Accelerates Hit Discovery." *ACS Chem. Biol.* 11: 2140-2148 (2016); the crystal structure PDB 5dw2 and related ligands described in Kharenko, O. A. et al. "RVX-297—a novel BD2 selective inhibitor of BET bromodomains." *Biochem. Biophys. Res. Commun.* 477: 62-67 (2016); the crystal structure PDB 5dlx; the crystal structure PDB Shis and related ligands described in Albrecht, B. K. et al. "Identification of a Benzoisoxazoloazepine Inhibitor (CPI-0610) of the Bromodomain and Extra-Terminal (BET) Family as a Candidate for Human Clinical Trials." *J. Med. Chem.* 59: 1330-1339 (2016); the crystal structure PDB 5ku3 and related ligands described in Crawford, T. D. et al. "Discovery of a Potent and Selective in Vivo Probe (GNE-272) for the Bromodomains of CBP/EP300". *J. Med. Chem.* 59: 10549-10563 (2016); the crystal structure PDB 51j2 and related ligands described in Bamborough, P. et al. "A Chemical Probe for the ATAD2 Bromodomain." *Angew. Chem. Int. Ed. Engl.* 55: 11382-11386 (2016); the crystal structure PDB 5dlx and related ligands described in Wang, L. "Fragment-based, structure-enabled discovery of novel pyridones and pyridone macrocycles as potent bromodomain and extra-terminal domain (BET) family bromodomain inhibitors". *J. Med. Chem.* 10.1021/acs.jmedchem.7b00017 (2017); WO 2015169962 A1 titled "Benzimidazole derivatives as BRD4 inhibitors and their preparation and use for the treatment of cancer" assigned to Boehringer Ingelheim International GmbH, Germany; and, WO 2011143669 A2 titled "Azolodiazepine derivatives and their preparation, compositions and methods for treating neoplasia, inflammatory disease and other disorders" assigned to Dana-Farber Cancer Institute, Inc, USA.

FIG. **8**T-**8**V present examples of ALK Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 2xb7 and 2xba and related ligands described in Bossi, R. T. et al. "Crystal Structures of Anaplastic Lymphoma Kinase in Complex with ATP Competitive Inhibitors" *Biochemistry* 49: 6813-6825 (2010); the crystal structures PDB 2yfx, 4ccb, 4ccu, amd 4cd0 snd related ligands described in Huang, Q. et al. "Design of Potent and Selective Inhibitors to Overcome Clinical Anaplastic Lymphoma Kinase Mutations Resistant to Crizotinib." *J. Med. Chem.* 57: 1170 (2014); the crystal structures PDB, 4cli, 4cmo, and 4cnh and related ligands described in Johnson, T. W. et al. "Discovery of (10R)-7-Amino-12-Fluoro-2,10,16-Trimethyl-15-Oxo-10,15,16,17-Tetrahydro-2H-8,4-(Metheno)Pyrazolo[4,3-H][2,5,11]Benzoxadiazacyclotetradecine-3-Carbonitrile (Pf-06463922), a Macrocyclic Inhibitor of Alk/Ros1 with Pre-Clinical Brain Exposure and Broad Spectrum Potency Against Alk-Resistant Mutations." *J. Med. Chem.* 57: 4720 (2014); the crystal structure PDB 4fny and related ligands described in Epstein, L. F. et al. "The R1275Q Neuroblastoma Mutant and Certain ATP-competitive Inhibitors Stabilize Alternative Activation Loop Conformations of Anaplastic Lymphoma Kinase." *J. Biol. Chem.* 287: 37447-37457 (2012). the crystal structure PDB 4dce and related ligands described in Bryan, M. C. et al "Rapid development of piperidine carboxamides as potent and selective anaplastic lymphoma kinase inhibitors. "*J. Med. Chem.* 55: 1698-1705 (2012); the crystal structure PDB 4joa and related ligands described in Gummadi, V. R. et al. "Discovery of 7-azaindole based anaplastic lymphoma kinase (ALK) inhibitors: wild type and mutant (L1196M) active compounds with unique binding mode." (2013) *Bioorg. Med. Chem. Lett.* 23: 4911-4918; and, the crystal structure PDB 5iui and related ligands described in Tu, C. H. et al. "Pyrazolylamine Derivatives Reveal the Conformational Switching between Type I and Type II Binding Modes of Anaplastic Lymphoma Kinase (ALK)." *J. Med. Chem.* 59: 3906-3919 (2016).

FIG. **8**W-**8**X present examples of BTK Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 3gen, 3piz and related ligands described in Marcotte, D. J. et al. "Structures of human Bruton's tyrosine kinase in active and inactive conformations suggest a mechanism of activation for TEC family kinases." *Protein Sci.* 19: 429-439 (2010) and Kuglstatter, A. et al. "Insights into the conformational flexibility of Bruton's tyrosine kinase from multiple ligand complex structures" *Protein Sci.* 20: 428-436" (2011); the crystal structure PDB 3ocs, 4ot6 and related ligands described in Lou, Y. et al. "Structure-Based Drug Design of RN486, a Potent and Selective Bruton's Tyrosine Kinase (BTK) Inhibitor, for the Treatment

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FIG. **8**Z-**8**AA present examples of TNIK Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2x7f; the crystal structures PDB 5ax9 and 5d7a; and, related ligands described in Masuda, M. et al. "TNIK inhibition abrogates colorectal cancer stemness." *Nat Commun* 7: 12586-12586 (2016).

FIG. **8**BB-**8**CC present examples of NTRK1, NTRK2, and NTRK3 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 4aoj and related ligands described in Wang, T. et al. "Discovery of Disubstituted Imidazo[4,5-B]Pyridines and Purines as Potent Trka Inhibitors." *ACS Med. Chem. Lett.* 3: 705 (2012); the crystal structures PDB 4pmm, 4pmp, 4pms and 4pmt and related ligands described in Stachel, S. J. et al. "Maximizing diversity from a kinase screen: identification of novel and selective pan-Trk inhibitors for chronic pain." *J. Med. Chem.* 57: 5800-5816 (2014); the crystal structures PDB 4yps and 4yne snd related ligands described in Choi, H. S. et al. "(R)-2-Phenylpyrrolidine Substituted Imidazopyridazines: A New Class of Potent and Selective Pan-TRK Inhibitors." *ACS Med. Chem. Lett.* 6: 562-567 (2015); the crystal structures PDB 4at5 and 4at3 and related ligands described in Bertrand, T. et al. "The Crystal Structures of Trka and Trkb Suggest Key Regions for Achieving Selective Inhibition." *J. Mol. Biol.* 423: 439 (2012); and, the crystal structures PDB 3v5q and 4ymj and related ligands described in Albaugh, P. et al. "Discovery of GNF-5837, a selective TRK Inhibitor with efficacy in rodent cancer tumor models." *ACS Med. Chem. Lett.* 3: 140-145 (2012) and Choi, H. S. et al. "(R)-2-Phenylpyrrolidine Substitute Imidazopyridazines: a New Class of Potent and Selective Pan-TRK Inhibitors." *ACS Med Chem Lett* 6: 562-567 (2015).

FIG. **8**DD-8EE present examples of FGFR1 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 3tto and 2fgi and related ligands described in Brison, Y. et al. "Functional and structural characterization of alpha-(1-2) branching sucrase derived from DSR-E glucansucrase." *J. Biol. Chem.* 287: 7915-7924 (2012) and Mohammadi, M. et al. "Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain." *EMBO J.* 17: 5896-5904 (1998); the crystal structure PDB 4fb3; the crystal structure PDB 4rwk and related ligands described in Harrison, C. et al. "Polyomavirus large T antigen binds symmetrical repeats at the viral origin in an asymmetrical manner." *J. Virol.* 87: 13751-13759 (2013); the crystal structure PDB 4rwl and related ligands described in Sohl, C. D. et al. "Illuminating the Molecular Mechanisms of Tyrosine Kinase Inhibitor Resistance for the FGFR1 Gatekeeper Mutation: The Achilles' Heel of Targeted Therapy." *ACS Chem. Biol.* 10: 1319-1329 (2015); the crystal structure PDB 4uwc; the crystal structure PDB 4v01 and related ligands described in Tucker, J. A. et al. "Structural Insights Into Fgfr Kinase Isoform Selectivity: Diverse Binding Modes of Azd4547 and Ponatinib in Complex with Fgfr1 and Fgfr4." *Structure* 22: 1764 (2014).; the crystal structure PDB 5a46 and related ligands described in Klein, T. et al. "Structural and Dynamic Insights Into the Energetics of Activation Loop Rearrangement in Fgfrl Kinase." *Nat. Commun.* 6: 7877 (2015); and, the crystal structure PDB 5ew8 and related ligands described in Patani, H. et al. "Landscape of activating cancer mutations in FGFR kinases and their differential responses to inhibitors in clinical use." *Oncotarget* 7: 24252-24268 (2016).

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FIG. **8**HH-**8**II present examples of MET Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 3qti and 3zcl; the crystal structures PDB 4xmo, 4xyf, and 3zcl and related ligands described in Peterson, E. A. et al. "Discovery of Potent and Selective 8-Fluorotriazolopyridine c-Met Inhibitors." *J. Med. Chem.* 58: 2417-2430 (2015) and Cui, J. J. et al. "Lessons from (S)-6-(1-(6-(1-Methyl-1H-Pyrazol-4-Yl)-[1, 2, 4]Triazolo[4,3-B]Pyridazin-3-Yl)Ethyl)Quinoline (Pf-04254644), an Inhibitor of Receptor Tyrosine Kinase C-met with High Protein Kinase Selectivity But Broad Phosphodiesterase Family Inhibition Leading to Myocardial Degeneration in Rats." *J. Med. Chem.* 56: 6651 (2013); the crystal structure PDB 5eyd and related ligands described in Boezio, A. A. et al. "Discovery of (R)-6-(1-(8-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one (AMG 337), a Potent and Selective Inhibitor of MET with High Unbound Target Coverage and Robust In Vivo Antitumor Activity." *J. Med. Chem.* 59: 2328-2342 (2016); the crystal structure PDB 3ce3 and related ligands described in Kim, K. S. et al. "Discovery of pyrrolopyridine-pyridone based inhibitors of Met kinase: synthesis, X-ray crystallographic analysis, and biological activities." *J Med. Chem.* 51: 5330-5341 (2008); the crystal structure PDB 2rfn and related ligands described in Bellon, S. F. et al. "c-Met inhibitors with novel binding mode show activity against several hereditary papillary renal cell carcinoma-related mutations." *J. Biol. Chem.* 283: 2675-2683 (2008); and, the crystal structure PDB 5dg5 and related ligands described in Smith, B. D. et al "Altiratinib Inhibits Tumor Growth, Invasion, Angiogenesis, and Microenvironment-Mediated Drug

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FIG. **8**GGGG presents examples of EPHA4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2y60 and related ligands described in Clifton, I. J. et al. "The Crystal Structure of Isopenicillin N Synthase with Delta((L)-Alpha-Aminoadipoyl)-(L)-Cysteinyl-(D)-Methionine Reveals Thioether Coordination to Iron", *Arch. Biochem. Biophys.* 516: 103 (2011) and the crystal structure PDB 2xyu and related ligands described in Van Linden, O. P et al. "Fragment Based Lead Discovery of Small Molecule Inhibitors for the Epha4 Receptor Tyrosine Kinase", *Eur. J. Med. Chem.* 47: 493 (2012).

FIG. **8**HHHH presents examples of EPHA7 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 3dko and related ligands described in Walker, J. R. et al. "Kinase domain of human ephrin type-a receptor 7 (epha7) in complex with ALW-II-49-7", to be published.

FIG. **8**IIII-**8**LLLL presents examples of EPHB4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2vx1 and related ligands described in Bardelle, C. et al. "Inhibitors of the Tyrosine Kinase Ephb4. Part 2: Structure-Based Discovery and Optimisation of 3,5-Bis Substituted Anilinopyrimidines", *Bioorg. Med. Chem. Lett.* 18: 5717(2008); the crystal structure PDB 2x9f and related ligands described in Bardelle, C. et al. "Inhibitors of the Tyrosine Kinase Ephb4. Part 3: Identification of Non-Benzodioxole-Based Kinase Inhibitors", *Bioorg. Med. Chem. Lett.* 20: 6242-6245 (2010); the crystal structure PDB 2xvd and related ligands described in Barlaam, B. et al. "Inhibitors of the Tyrosine Kinase Ephb4. Part 4: Discovery and Optimization of a Benzylic Alcohol Series", *Bioorg. Med. Chem. Lett.* 21: 2207 (2011); the crystal structure PDB 3zew and related ligands described in Overman, R. C. et al. "Completing the Structural Family Portrait of the Human Ephb Tyrosine Kinase Domains", *Protein Sci.* 23: 627 (2014); the crystal structure PDB 4aw5 and related ligands described in Kim, M. H. et al. "The Design, Synthesis, and Biological Evaluation of Potent Receptor Tyrosine Kinase Inhibitors", *Bioorg. Med. Chem. Lett.* 22: 4979 (2012); the crystal structure PDB 4bb4 and related ligands described in Vasbinder, M. M. et al. "Discovery and Optimization of a Novel Series of Potent Mutant B-Raf V600E Selective Kinase Inhibitors" *J. Med. Chem.* 56: 1996.", (2013); the crystal structures PDB 2vwu, 2vwv and 2vww and related ligands described in Bardelle, C. et al "Inhibitors of the Tyrosine Kinase Ephb4. Part 1: Structure-Based Design and Optimization of a Series of 2,4-Bis-Anilinopyrimidines", *Bioorg. Med. Chem. Lett.* 18: 2776-2780 (2008); the crystal structures PDB 2vwx, 2vwy, and 2vwz and related ligands described in Bardelle, C. et al. "Inhibitors of the Tyrosine Kinase Ephb4. Part 2: Structure-Based Discovery and Optimisation of 3,5-Bis Substituted Anilinopyrimidines", *Bioorg. Med. Chem. Lett.* 18: 5717 (2008); and, the crystal structure PDB 2vxo and related ligands described in Welin, M. et al. "Substrate Specificity and Oligomerization of Human Gmp Synthetas", *J. Mol. Biol.* 425: 4323 (2013).

FIG. **8**MMMM presents examples of ERBB2 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure and related ligands described in Aertgeerts, K. et al "Structural Analysis of the Mechanism of Inhibition and Allosteric Activation of the Kinase Domain of HER2 Protein", *J. Biol. Chem.* 286: 18756-18765 (2011) and the crystal structure and related ligands described in Ishikawa, T. et al. "Design and Synthesis of Novel Human Epidermal Growth Factor Receptor 2 (HER2)/Epidermal Growth Factor Receptor (EGFR) Dual Inhibitors Bearing a Pyrrolo[3,2-d]pyrimidine Scaffold" *J Med. Chem.* 54: 8030-8050 (2011).

FIG. **8**NNNN presents examples of ERBB3 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Littlefield, P. et al. "An ATP-Competitive Inhibitor Modulates the Allosteric Function of the HER3 Pseudokinase", *Chem. Biol.* 21: 453-458 (2014).

FIG. **8**OOOO presents examples ERBB4 Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Qiu, C. et al. "Mechanism of Activation and Inhibition of the HER4/ErbB4 Kinase", *Structure* 16: 460-467 (2008) and Wood, E. R. et al. "6-Ethynylthieno[3,2-d]- and 6-ethynylthieno[2,3-d]pyrimidin-4-anilines as tunable covalent modifiers of ErbB kinases", *Proc. Natl. Acad. Sci.* Usa 105: 2773-2778 (2008).

FIG. **8**PPPP-**8**QQQQ present examples of FES Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Filippakopoulos, P. et al "Structural Coupling of SH2-Kinase Domains Links Fes and Abl Substrate Recognition and Kinase Activation." *Cell* 134: 793-803 (2008) and Hellwig, S. et al. "Small-Molecule Inhibitors of the c-Fes Protein-Tyrosine Kinase", *Chem. Biol.* 19: 529-540 (2012).

FIG. **8**RRRR presents examples of FYN Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, Kinoshita, T. et. al. "Structure of human Fyn kinase domain complexed with staurosporine", *Biochem. Biophys. Res. Commun.* 346: 840-844 (2006).

FIG. **8**SSSS-**8**VVVV present examples of GSG2 (Haspin) Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structures PDB 3e7v, PDB 3f2n, 3fmd and related ligands described in Filippakopoulos, P. et al. "Crystal Structure of Human Haspin with a pyrazolo-pyrimidine ligand", to be published; the crystal structure PDB 3iq7 and related ligands described in Eswaran, J. et al. "Structure and functional characterization of the atypical human kinase haspin", *Proc. Natl. Acad. Sci. USA* 106: 20198-20203 (2009); and, the crystal structure PDB 4qtc and related ligands described in Chaikuad, A. et al. "A unique inhibitor binding site in ERK1/2 is associated with slow binding kinetics", *Nat. Chem. Biol.* 10: 853-860 (2014).

FIG. **8**WWWW-**8**AAAAA present examples of HCK Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB lqcf and related ligands described in Schindler, T. et al. "Crystal structure of Hck in complex with a Src family-selective tyrosine kinase inhibitor", *Mol. Cell* 3: 639-648 (1999); the crystal structure PDB 2cOi and 2 cOt and related ligands described in Burchat, A. et al. "Discovery of A-770041, a Src-Family Selective Orally Active Lck Inhibitor that Prevents Organ Allograft Rejection", *Bioorg. Med. Chem. Lett.* 16: 118 (2006); the crystal structure PDB 2hk5 and related ligands described in Sabat, M. et al. "The development of 2-benzimidazole substituted pyrimidine based inhibitors of lymphocyte specific kinase (Lck)", *Bioorg. Med. Chem. Lett.* 16: 5973-5977 (2006); the crystal structures PDB 3vry, 3vs3, 3vs6, and 3vs7 and related ligands described in Saito, Y. et al. "A Pyrrolo-Pyrimidine Derivative Targets Human Primary AML Stem Cells in Vivo", *Sci Transl Med* 5: 181ra52-181ra52 (2013); and, the crystal structure PDB 41ud and related ligands described in Parker, L. J. et al "Kinase crystal identification and ATP-competitive inhibitor screening using the fluorescent ligand SKF86002". *Acta Crystallogr., Sect. D* 70: 392-404 (2014).

FIG. **8**BBBBB-**8**FFFFF present examples of IGF1R Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2oj9 and related ligands described in Velaparthi, U. et al. "Discovery and initial SAR of 3-(1H-benzo[d]imidazol-2-yl)pyridin-2(1H)-ones as inhibi-

tors of insulin-like growth factor 1-receptor (IGF-1R)", *Bioorg. Med. Chem. Lett.* 17: 2317-2321 (2007); the crystal structure PDB 3i81 and related ligands described in Wittman, M. D. et al. "Discovery of a 2,4-disubstituted pyrrolo [1,2-f][1,2,4]triazine inhibitor (BMS-754807) of insulin-like growth factor receptor (IGF-1R) kinase in clinical development.", *J. Med. Chem.* 52: 7360-7363 (2009); the crystal structure PDB 3nw5 and related ligands described in Sampognaro, A. J. et al. "Proline isosteres in a series of 2,4-disubstituted pyrrolo[1,2-f][1,2,4]triazine inhibitors of IGF-1R kinase and IR kinase", *Bioorg. Med. Chem. Lett.* 20: 5027-5030 (2010); the crystal structure PDB 3qqu and related ligands described in Buchanan, J. L. et al. "Discovery of 2,4-bis-arylamino-1,3-pyrimidines as insulin-like growth factor-1 receptor (IGF-1R) inhibitors", *Bioorg. Med. Chem. Lett.* 21: 2394-2399 (2011); the crystal structure PDB 4d2r and related ligands described in Kettle, J. G. et al. "Discovery and Optimization of a Novel Series of Dyrk1B Kinase Inhibitors to Explore a Mek Resistance Hypothesis". *J. Med. Chem.* 58: 2834 (2015); the crystal structure PDB 3fxq and related ligands described in Monferrer, D. et al. "Structural studies on the full-length LysR-type regulator TsaR from *Comamonas testosteroni* T-2 reveal a novel open conformation of the tetrameric LTTR fold", *Mol. Microbiol.* 75: 1199-1214 (2010); the crystal structure PDB 5fxs and related ligands described in Degorce, S. et al. "Discovery of Azd9362, a Potent Selective Orally Bioavailable and Efficacious Novel Inhibitor of Igf-R1", to be published; the crystal structure PDB 2zm3 and related ligands described in Mayer, S. C. et al. "Lead identification to generate isoquinolinedione inhibitors of insulin-like growth factor receptor (IGF-1R) for potential use in cancer treatment", *Bioorg. Med. Chem. Lett.* 18: 3641-3645 (2008); the crystal structure PDB 3f5p and related ligands described in "Lead identification to generate 3-cyanoquinoline inhibitors of insulin-like growth factor receptor (IGF-1R) for potential use in cancer treatment" *Bioorg. Med. Chem. Lett.* 19: 62-66 (2009); the crystal structure PDB 31vp and related ligands described in Nemecek, C. et al. "Design of Potent IGF1-R Inhibitors Related to Bis-azaindoles" *Chem. Biol. Drug Des.* 76: 100-106 (2010); the crystal structure PDB 3o23 and related ligands described in Lesuisse, D. et al. "Discovery of the first non-ATP competitive IGF-1R kinase inhibitors: Advantages in comparison with competitive inhibitors", *Bioorg. Med. Chem. Lett.* 21: 2224-2228 (2011); the crystal structure PDB 3d94 and related ligands described in Wu, J. et al. "Small-molecule inhibition and activation-loop transphosphorylation of the IGF1 receptor", *Embo J.* 27: 1985-1994 (2008); and, the crystal structure PDB 5hzn and related ligands described in Stauffer, F. et al. "Identification of a 5-[3-phenyl-(2-cyclic-ether)-methylether]-4-aminopyrrolo [2,3-d]pyrimidine series of IGF-1R inhibitors", *Bioorg. Med. Chem. Lett.* 26: 2065-2067 (2016).

FIG. **8**GGGGG-**8**JJJJJ present examples of INSR Targeting Ligands wherein R is the point at which the Linker is attached. For additional examples and related ligands, see, the crystal structure PDB 2z8c and related ligands described in Katayama, N. et al. "Identification of a key element for hydrogen-bonding patterns between protein kinases and their inhibitors", *Proteins* 73: 795-801 (2008); the crystal structure PDB 3ekk and related ligands described in Chamberlain, S. D. et al. "Discovery of 4,6-bis-anilino-1H-pyrrolo [2,3-d]pyrimidines: Potent inhibitors of the IGF-1R receptor tyrosine kinase", (2009) *Bioorg. Med. Chem. Lett.* 19: 469-473; the crystal structure PDB 3ekn and related ligands described in Chamberlain, S. D. et al. "Optimization of 4,6-bis-anilino-1H-pyrrolo[2,3-d]pyrimidine IGF-1R tyrosine kinase inhibitors towards JNK selectivity", *Bioorg. Med. Chem. Lett.* 19: 360-364 (2009); the crystal structure PDB 5els and related ligands described in Sanderson, M. P. et al. "BI 885578, a Novel IGF1R/INSR Tyrosine Kinase Inhibitor with Pharmacokinetic Properties That Dissociate Antitumor Efficacy and Perturbation of Glucose Homeostasis" *Mol. Cancer Ther.* 14: 2762-2772 ", (2015); the crystal structure PDB 3eta and related ligands described in Patnaik, S. et al. "Discovery of 3,5-disubstituted-1H-pyrrolo[2,3-b] pyridines as potent inhibitors of the insulin-like growth factor-1 receptor (IGF-1R) tyrosine kinase", *Bioorg. Med. Chem. Lett.* 19: 3136-3140 (2009); the crystal structure PDB Shhw and related ligands described in Stauffer, F. et al. "Identification of a 5-[3-phenyl-(2-cyclic-ether)-methylether]-4-aminopyrrolo[2,3-d]pyrimidine series of IGF-1R inhibitors", *Bioorg. Med. Chem. Lett.* 26: 2065-2067 (2016); and, the crystal structure PDB 4ibm and related ligands described in Anastassiadis, T. et al. "A highly selective dual insulin receptor (IR)/insulin-like growth factor 1 receptor (IGF-1R) inhibitor derived from an extracellular signal-regulated kinase (ERK) inhibitor", *J Biol. Chem.* 288: 28068-28077 (2013).

FIG. **8**KKKKK-**8**PPPPP present examples of HBV Targeting Ligands wherein R is the point at which the Linker is attached, Y is methyl or isopropyl, and X is N or C. For additional examples and related ligands, see, Weber, O.; et al. "Inhibition of human hepatitis B virus (HBV) by a novel non-nucleosidic compound in a transgenic mouse model." *Antiviral Res.* 54, 69-78 (2002); Deres, K.; et al. "Inhibition of hepatitis B virus replication by drug-induced depletion of nucleocapsids." *Science,* 299, 893-896 (2003); Stray, S. J.; Zlotnick, A. "BAY 41-4109 has multiple effects on Hepatitis B virus capsid assembly." *J. Mol. Recognit.* 19, 542-548 (2006); Stray, S. J.; et al. "heteroaryldihydropyrimidine activates and can misdirect hepatitis B virus capsid assembly." *Proc. Natl. Acad. Sci. U.S.A,* 102, 8138-8143 (2005); Guan, H.; et al. "The novel compound Z060228 inhibits assembly of the HBV capsid." *Life Sci.* 133, 1-7 (2015); Wang, X. Y.; et al. "In vitro inhibition of HBV replication by a novel compound, GLS4, and its efficacy against adefovir-dipivoxil-resistant HBV mutations." *Antiviral Ther.* 17, 793-803 (2012); Klumpp, K.; et al. "High-resolution crystal structure of a hepatitis B virus replication inhibitor bound to the viral core protein." 112, 15196-15201 (2015); Qiu, Z.; et al. "Design and synthesis of orally bioavailable 4-methyl heteroaryldihydropyrimidine based hepatitis B virus (HBV) capsid inhibitors." *J. Med. Chem.* 59, 7651-7666 (2016); Zhu, X.; et al. "2,4-Diaryl-4,6,7,8-tetrahydroquinazolin-5 (1H)-one derivatives as anti-HBV agents targeting at capsid assembly." *Bioorg. Med. Chem. Lett.* 20, 299-301 (2010); Campagna, M. R.; et al. "Sulfamoylbenzamide derivatives inhibit the assembly of hepatitis B virus nucleocapsids." *J. Virol.* 87, 6931-6942 (2013); Campagna, M. R.; et al. "Sulfamoylbenzamide derivatives inhibit the assembly of hepatitis B virus nucleocapsids." *J. Virol.* 87, 6931-6942 (2013); WO 2013096744 A1 titled "Hepatitis B antivial agents"; WO 2015138895 titled "Hepatitis B core protein allosteric modulators"; Wang, Y. J.; et al. "A novel pyridazinone derivative inhibits hepatitis B virus replication by inducing genome-free capsid formation." *Antimicrob. Agents Chemother.* 59, 7061-7072 (2015); WO 2014033167 titled "Fused bicyclic sulfamoyl derivatives for the treatment of hepatitis"; U.S. 20150132258 titled "Azepane derivatives and methods of treating hepatitis B infections"; and, WO 2015057945 "Hepatitis B viral assembly effector".

FIG. **9** is a dendrogram of the human bromodomain family of proteins organized into eight sub families, which

are involved in epigenetic signaling and chromatin biology. Any of the proteins of the bromodomain family in FIG. **9** can be selected as a Target Protein according to the present invention.

DETAILED DESCRIPTION

I. Definitions

Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

The compounds in any of the Formulas described herein may be in the form of a racemate, enantiomer, mixture of enantiomers, diastereomer, mixture of diastereomers, tautomer, N-oxide, isomer; such as rotamer, as if each is specifically described unless specifically excluded by context.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

The present invention includes compounds of Formula I, Formula II, Formula III, and Formula IV with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, and ^{125}I respectively. In one non-limiting embodiment, isotopically labelled compounds can be used in metabolic studies (with, for example ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F labeled compound may be particularly desirable for PET or SPECT studies. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is 90, 95 or 99% or more enriched in an isotope at any location of interest. In one non-limiting embodiment, deuterium is 90, 95 or 99% enriched at a desired location.

In one non-limiting embodiment, the substitution of a hydrogen atom for a deuterium atom can be provided in any compound of Formula I, Formula II, Formula III, or Formula IV. In one non-limiting embodiment, the substitution of a hydrogen atom for a deuterium atom independently occurs within one or more groups selected from any of Rs and variables described herein, Linker, and Targeting Ligand. For example, when any of the groups are, or contain for example through substitution, methyl, ethyl, or methoxy, the alkyl residue may be deuterated (in non-limiting embodiments, CDH_2, CD_2H, CD_3, CH_2CD_3, CD_2CD_3, $CHDCH_2D$, CH_2CD_3, $CHDCHD_2$, $OCDH_2$, OCD_2H, or OCD_3 etc.). In certain other embodiments, when two substituents are combined to form a cycle the unsubstituted carbons may be deuterated.

The compound of the present invention may form a solvate with a solvent (including water). Therefore, in one non-limiting embodiment, the invention includes a solvated form of the compound. The term "solvate" refers to a molecular complex of a compound of the present invention (including a salt thereof) with one or more solvent molecules. Non-limiting examples of solvents are water, ethanol, isopropanol, dimethyl sulfoxide, acetone and other common organic solvents. The term "hydrate" refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent may be isotopically substituted, e.g. D_2O, d6-acetone, d_6-DMSO. A solvate can be in a liquid or solid form.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, —(C═O)NH_2 is attached through carbon of the carbonyl (C═O) group.

"Alkyl" is a branched or straight chain saturated aliphatic hydrocarbon group. In one non-limiting embodiment, the alkyl group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one non-limiting embodiment, the alkyl contains from 1 to about 8 carbon atoms. In certain embodiments, the alkyl is C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, or C_1-C_6. The specified ranges as used herein indicate an alkyl group having each member of the range described as an independent species. For example, the term C_1-C_6 alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species and therefore each subset is considered separately disclosed. For example, the term C_1-C_4 alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, tert-pentyl, neopentyl, n-hexyl, 2-methylpentane, 3-methylpentane, 2,2-dimethylbutane, and 2,3-dimethylbutane. In an alternative embodiment, the alkyl group is optionally substituted. The term "alkyl" also encompasses cycloalkyl or carbocyclic groups. For example, when a term is used that includes "alk" then "cycloalkyl" or "carbocyclic" can be considered part of the definition, unless unambiguously excluded by the context. For example and without limitation, the terms alkyl, alkoxy, haloalkyl, etc. can all be considered to include the cyclic forms of alkyl, unless unambiguously excluded by context.

"Alkenyl" is a linear or branched aliphatic hydrocarbon groups having one or more carbon-carbon double bonds that may occur at a stable point along the chain. The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkenyl radicals include, but are not limited to ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The term "alkenyl" also embodies "cis" and "trans" alkenyl geometry, or alternatively, "E" and "Z" alkenyl geometry. In an alternative embodiment, the alkenyl group is optionally substituted. The term "Alkenyl" also encompasses cycloalkyl or carbocyclic groups possessing at least one point of unsaturation.

"Alkynyl" is a branched or straight chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain. The specified ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. In an alternative embodiment, the alkynyl group is optionally substituted. The term "Alkynyl" also encompasses cycloalkyl or carbocyclic groups possessing at least one triple bond.

"Alkylene" is a bivalent saturated hydrocarbon. Alkylenes, for example, can be a 1, 2, 3, 4, 5, 6, 7 to 8 carbon moiety, 1 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_1-C_2alkylene, C_1-C_3alkylene, C_1-C_4alkylene, C_1-C_6alkylene, or C_1-C_6alkylene.

"Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_2-C_4alkenylene.

"Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example C_2-C_4alkynylene.

"Halo" and "Halogen" refers to fluorine, chlorine, bromine or iodine.

"Haloalkyl" is a branched or straight-chain alkyl groups substituted with 1 or more halo atoms described above, up to the maximum allowable number of halogen atoms. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perhaloalkyl" means an alkyl group having all hydrogen atoms replaced with halogen atoms. Examples include but are not limited to, trifluoromethyl and pentafluoroethyl.

"Chain" indicates a linear chain to which all other chains, long or short or both, may be regarded as being pendant. Where two or more chains could equally be considered to be the main chain, "chain" refers to the one which leads to the simplest representation of the molecule.

"Haloalkoxy" indicates a haloalkyl group as defined herein attached through an oxygen bridge (oxygen of an alcohol radical).

"Heterocycloalkyl" is an alkyl group as defined herein substituted with a heterocyclo group as defined herein.

"Arylalkyl" is an alkyl group as defined herein substituted with an aryl group as defined herein.

"Heteroarylalkyl" is an alkyl group as defined herein substituted with a heteroaryl group as defined herein.

As used herein, "aryl" refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system ("C_{6-14} aryl"). In some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; e.g., phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; e.g., anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. The one or more fused carbocyclyl or heterocyclyl groups can be 4 to 7 or 5 to 7-membered saturated or partially unsaturated carbocyclyl or heterocyclyl groups that optionally contain 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen, phosphorus, sulfur, silicon and boron, to form, for example, a 3,4-methylenedioxyphenyl group. In one non-limiting embodiment, aryl groups are pendant. An example of a pendant ring is a phenyl group substituted with a phenyl group. In an alternative embodiment, the aryl group is optionally substituted as described above. In certain embodiments, the aryl group is an unsubstituted C_6-14 aryl. In certain embodiments, the aryl group is a substituted C_6-14 aryl. An aryl group may be optionally substituted with one or more functional groups that include but are not limited to, halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, and heterocyclo.

The term "heterocyclyl" (or "heterocyclo") includes saturated, and partially saturated heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heterocyclic rings comprise monocyclic 3-8 membered rings, as well as 5-16 membered bicyclic ring systems (which can include bridged fused and spiro-fused bicyclic ring systems). It does not include rings containing —O—O—. —O—S— or —S—S— portions. Said "heterocyclyl" group may be optionally substituted, for example, with 1, 2, 3, 4 or more substituents that include but are not limited to, hydroxyl, Boc, halo, haloalkyl, cyano, alkyl, aralkyl, oxo, alkoxy, and amino. Examples of saturated heterocyclo groups include saturated 3- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include but are not limited to, dihydrothienyl, dihydropyranyl, dihydrofuryl, and dihydrothiazolyl. Examples of partially saturated and saturated heterocyclo groups include but are not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-

triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

Heterocyclo groups also include radicals where heterocyclic radicals are fused/condensed with aryl or heteroaryl radicals: such as unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indoline, isoindoline, unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms.

The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include but are not limited to, unsaturated 5 to 6 membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, such as pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "optionally substituted" denotes the substitution of a group herein by a moiety including, but not limited to, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkenyl, C_1-C_{12} heterocycloalkyl, C_3-C_{12} heterocycloalkenyl, C_1-C_{10} alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, arylamino, diarylamino, C_1-C_{10} alkylsulfonamino, arylsulfonamino, C_1-C_{10} alkylimino, arylimino, C_1-C_{10} alkylsulfonimino, arylsulfonimino, hydroxyl, halo, thio, C_1-C_{10} alkylthio, arylthio, C_1-C_{10} alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, guanidine, ureido, cyano, nitro, azido, acyl, thioacyl, acyloxy, carboxyl, and carboxylic ester.

In one alternative embodiment any suitable group may be present on a "substituted" or "optionally substituted" position if indicated that forms a stable molecule and meets the desired purpose of the invention and includes, but is not limited to, e.g., halogen (which can independently be F, Cl, Br or I); cyano; hydroxyl; nitro; azido; alkanoyl (such as a C_2-C_6 alkanoyl group); carboxamide; alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy such as phenoxy; thioalkyl including those having one or more thioether linkages; alkylsulfinyl; alkylsulfonyl groups including those having one or more sulfonyl linkages; aminoalkyl groups including groups having more than one N atoms; aryl (e.g., phenyl, biphenyl, naphthyl, or the like, each ring either substituted or unsubstituted); arylalkyl having for example, 1 to 3 separate or fused rings and from 6 to about 14 or 18 ring carbon atoms, with benzyl being an exemplary arylalkyl group; arylalkoxy, for example, having 1 to 3 separate or fused rings with benzyloxy being an exemplary arylalkoxy group; or a saturated or partially unsaturated heterocycle having 1 to 3 separate or fused rings with one or more N, O or S atoms, or a heteroaryl having 1 to 3 separate or fused rings with one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, isoquinolinyl, quinazolinyl, pyridyl, pyrazinyl, pyrimidinyl, furanyl, pyrrolyl, thienyl, thiazolyl, triazinyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl. Such groups may be further substituted, e.g. with hydroxy, alkyl, alkoxy, halogen and amino. In certain embodiments "optionally substituted" includes one or more substituents independently selected from halogen, hydroxyl, amino, cyano, —CHO, —COOH, —$CONH_2$, alkyl including C_1-C_6alkyl, alkenyl including C_2-C_6alkenyl, alkynyl including C_2-C_6alkynyl, —C_1-C_6alkoxy, alkanoyl including C_2-C_6alkanoyl, C_1-C_6alkylester, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, haloalkyl including C_1-C_6haloalkyl, hydoxyC_1-C_6alkyl, ester, carbamate, urea, sulfonamide, —C_1-C_6alkyl(heterocyclo), C_1-C_6alkyl(heteroaryl), —C_1-C_6alkyl(C_3-C_7cycloalkyl), O—C_1-C_6alkyl(C_3-C_7cycloalkyl), $B(OH)_2$, phosphate, phosphonate and haloalkoxy including C_1-C_6haloalkoxy.

"Aliphatic" refers to a saturated or unsaturated, straight, branched, or cyclic hydrocarbon. "Aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties, and thus incorporates each of these definitions. In one embodiment, "aliphatic" is used to indicate those aliphatic groups having 1-20 carbon atoms. The aliphatic chain can be, for example, mono-unsaturated, di-unsaturated, tri-unsaturated, or polyunsaturated, or alkynyl. Unsaturated aliphatic groups can be in a cis or trans configuration. In one embodiment, the aliphatic group contains from 1 to about 12 carbon atoms, more generally from 1 to about 6 carbon atoms or from 1 to about 4 carbon atoms. In one embodiment, the aliphatic group contains from 1 to about 8 carbon atoms. In certain embodiments, the aliphatic group is C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5 or C_1-C_6. The specified ranges as used herein indicate an aliphatic group having each member of the range described as an independent species. For example, the term C_1-C_6 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term C_1-C_4 aliphatic as used herein indicates a straight or branched alkyl, alkenyl, or alkynyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. In one embodiment, the aliphatic group is substituted with one or more functional groups that results in the formation of a stable moiety.

The term "heteroaliphatic" refers to an aliphatic moiety that contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate, nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. "Heteroaliphatic" is intended herein to include, but is not limited to, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, and heterocycloalkynyl moieties. In one embodiment, "heteroaliphatic" is used to indicate a heteroaliphatic group (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-20 carbon atoms. In one embodiment, the heteroaliphatic group is optionally substituted in a manner that results in the

formation of a stable moiety. Nonlimiting examples of heteroaliphatic moieties are polyethylene glycol, polyalkylene glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, —O-alkyl-O-alkyl, alkyl-O-haloalkyl, etc.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, implants, particles, spheres, creams, ointments, suppositories, inhalable forms, transdermal forms, buccal, sublingual, topical, gel, mucosal, and the like. A "dosage form" can also include an implant, for example an optical implant.

An "effective amount" as used herein, means an amount which provides a therapeutic or prophylactic benefit.

As used herein "endogenous" refers to any material from or produced inside an organism, cell, tissue or system.

As used herein, the term "exogenous" refers to any material introduced from or produced outside an organism, cell, tissue or system.

By the term "modulating," as used herein, is meant mediating a detectable increase or decrease in the level of a response in a subject compared with the level of a response in the subject in the absence of a treatment or compound, and/or compared with the level of a response in an otherwise identical but untreated subject. The term encompasses perturbing and/or affecting a native signal or response thereby mediating a beneficial therapeutic response in a subject, preferably, a human.

"Parenteral" administration of an immunogenic composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, or infusion techniques.

As used herein, the terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

To "treat" a disease as the term is used herein, means to reduce the frequency or severity of at least one sign or symptom of a disease or disorder experienced by a subject.

Ranges: throughout this disclosure, various aspects of the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and should not be construed as a limitation on the scope of the invention. The description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

As used herein, "pharmaceutical compositions" are compositions comprising at least one active agent, and at least one other substance, such as a carrier. "Pharmaceutical combinations" are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat any disorder described herein.

As used herein, "pharmaceutically acceptable salt" is a derivative of the disclosed compound in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are typical, where practicable. Salts of the present compounds further include solvates of the compounds and of the compound salts.

Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC—(CH_2)n-COOH where n is 0-4, and the like, or using a different acid that produces the same counterion. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

The term "carrier" applied to pharmaceutical compositions/combinations of the invention refers to a diluent, excipient, or vehicle with which an active compound is provided.

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition/combination that is generally safe, non-toxic and neither biologically nor otherwise inappropriate for administration to a host, typically a human. In one embodiment, an excipient is used that is acceptable for veterinary use.

A "patient" or "host" or "subject" is a human or non-human animal in need of treatment or prevention of any of the disorders as specifically described herein, for example that is modulated by a natural (wild-type) or modified (non-wild type) protein that can be degraded according to the present invention, resulting in a therapeutic effect. Typically, the host is a human. A "host" may alternatively refer

to for example, a mammal, primate (e.g., human), cow, sheep, goat, horse, dog, cat, rabbit, rat, mice, fish, bird and the like.

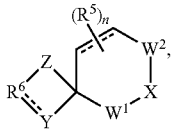
A "therapeutically effective amount" of a pharmaceutical composition/combination of this invention means an amount effective, when administered to a host, to provide a therapeutic benefit such as an amelioration of symptoms or reduction or diminution of the disease itself.

II. Compounds

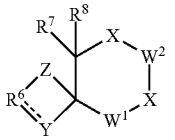
Formula I and Formula II

In one aspect of the present invention a Degronimer of Formula I or Formula II is provided:

(I)



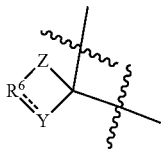
(II)



or a pharmaceutically acceptable salt, N-oxide, isotopic derivative or prodrug, optionally in a pharmaceutically acceptable carrier to create a pharmaceutical composition; and the variables are as described above;

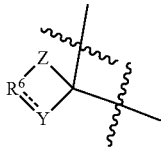
and wherein the contiguous atoms of R^6 can be attached through a single or double bond;

or in an alternative embodiment

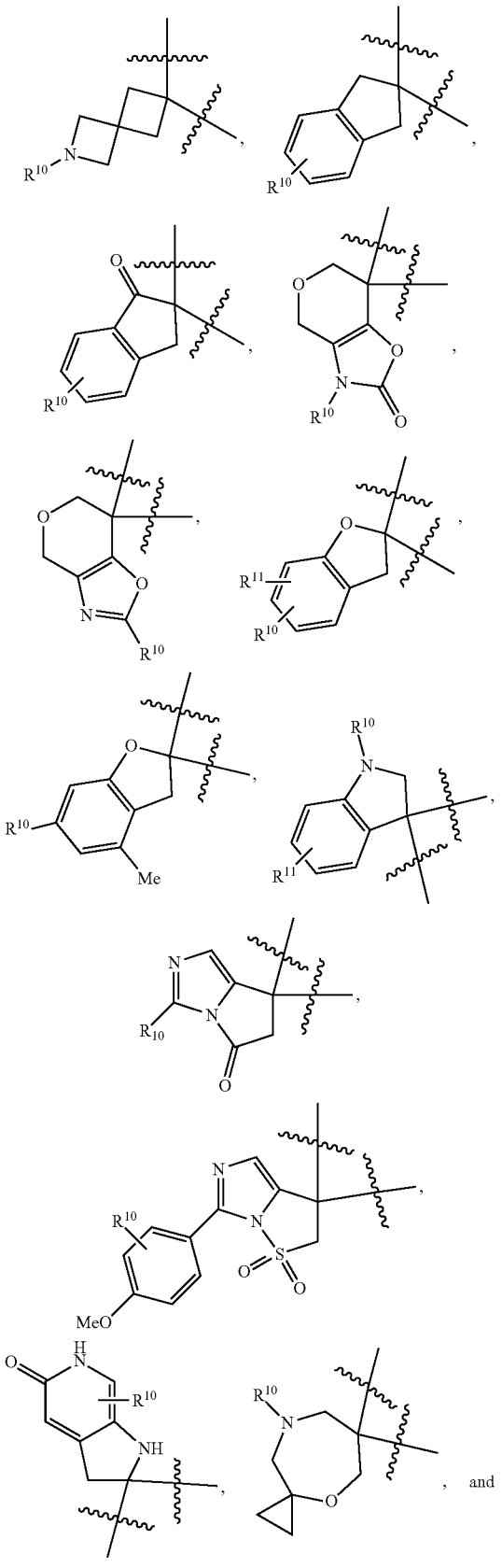


forms a bicyclic moiety which is substituted with R^{10} and optionally substituted with one or more groups independently selected from R^{11} and oxo;

Non-limiting examples of bicyclic



Y moieties include:



and

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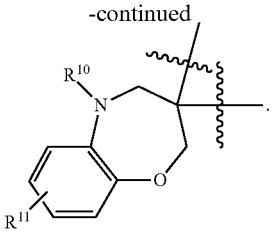
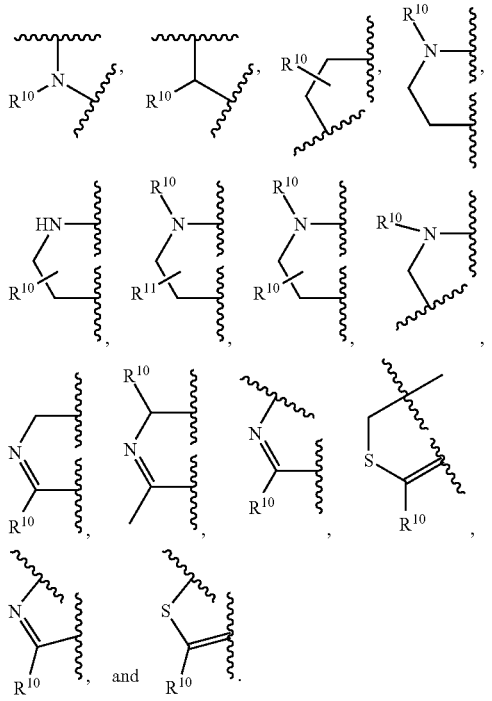
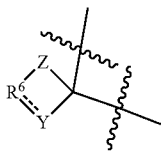


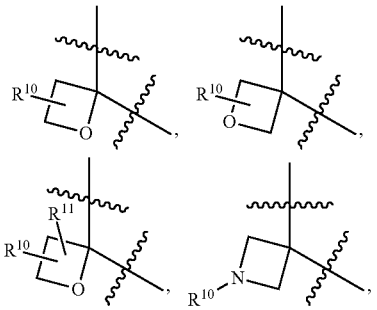
Non-limiting examples of R^6 include:



Non-limiting examples of



include:



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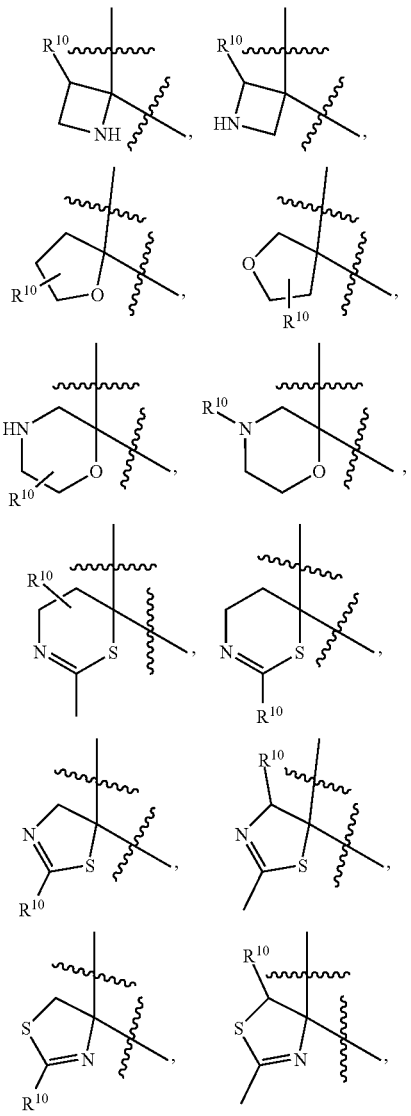

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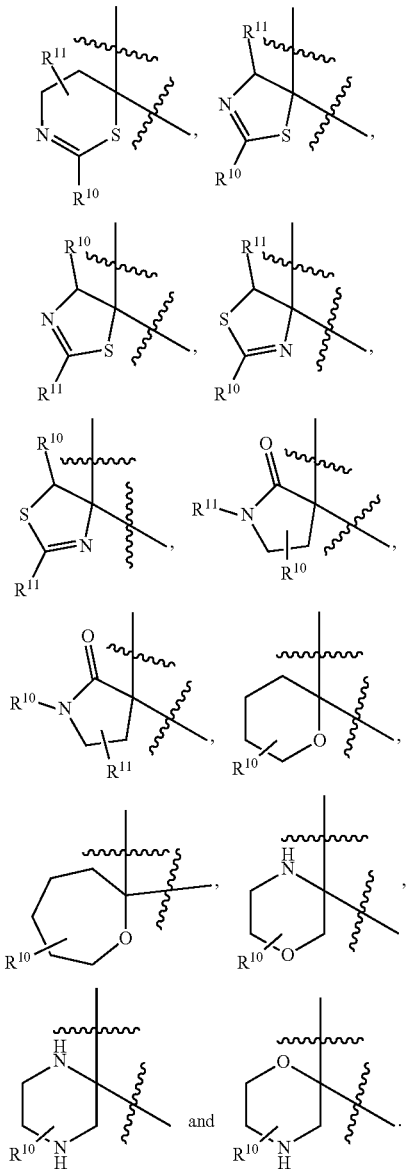
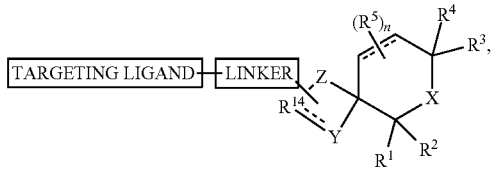
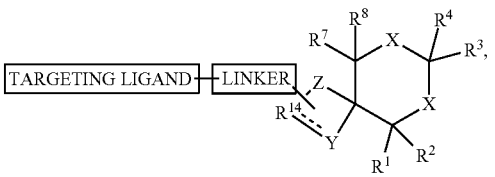


In one embodiment, the compound is selected from:

(Ia)



(IIa)



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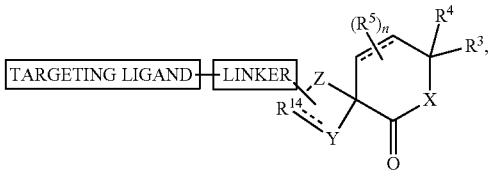
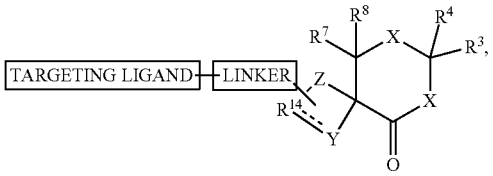
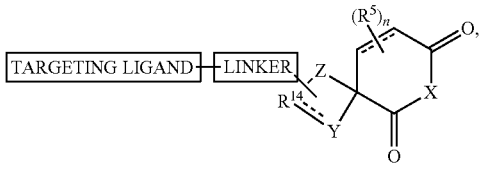
(Ib)



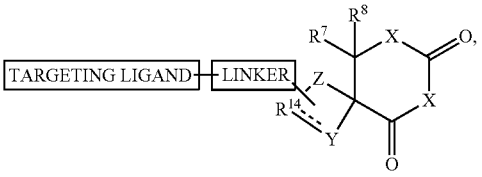
(IIb)



(Ic)



(IIc)



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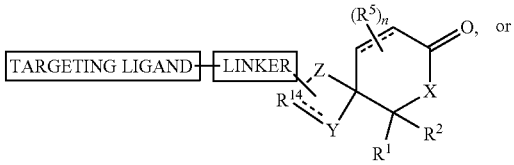
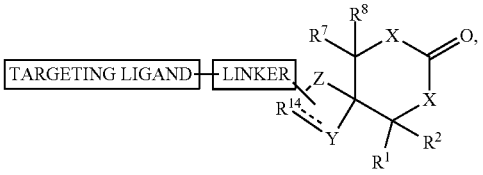


or

(IId)

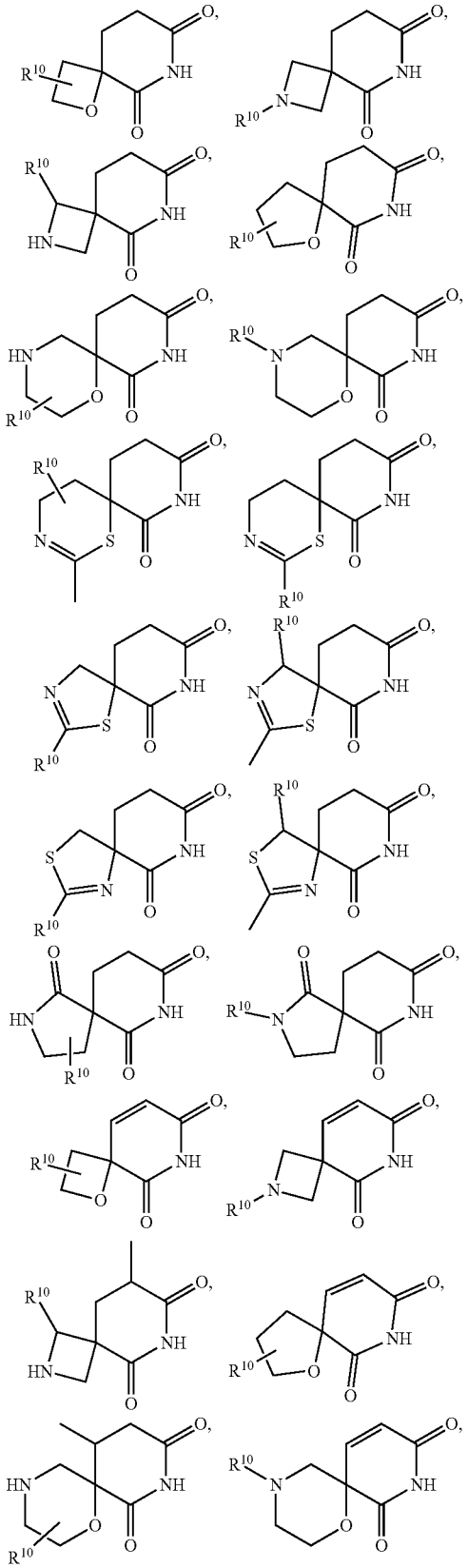


or a pharmaceutically acceptable salt, N-oxide, isotopic derivative or prodrug, optionally in a pharmaceutically acceptable carrier to create a pharmaceutical composition;

wherein:

R^{14} is a bond (i.e.: Y and Z are directly linked to form a 3 membered ring) or R^{14} is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom as long as the resultant molecule has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable, and wherein the ring atoms are optionally substituted with R^{11}.

Non-limiting examples of compounds of Formula I include:



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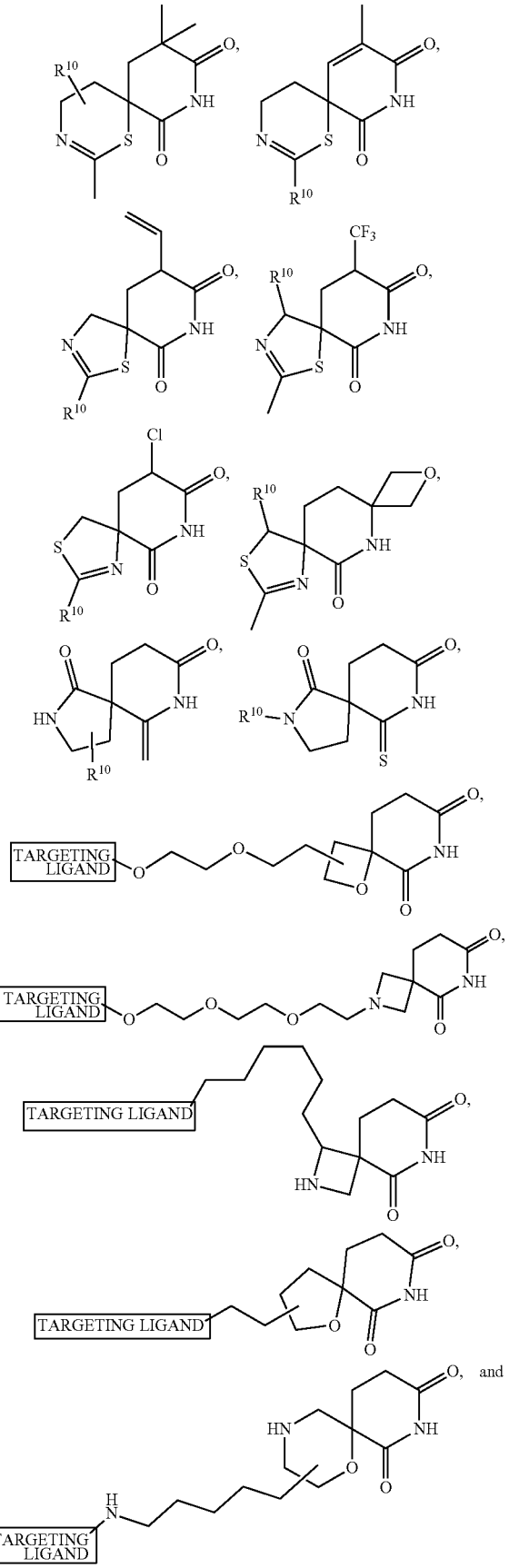

and

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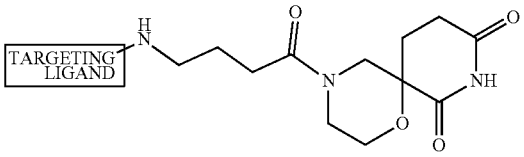

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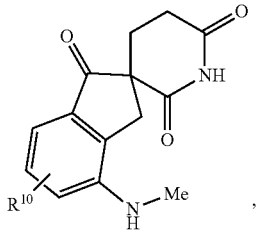
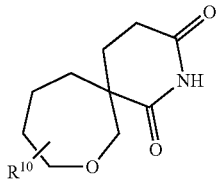


Additional non-limiting examples of compounds of Formula I include:



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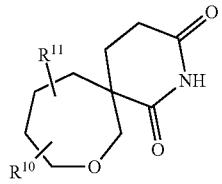

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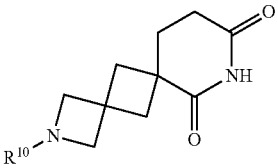

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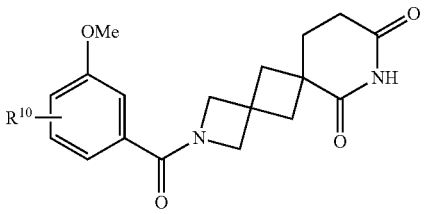

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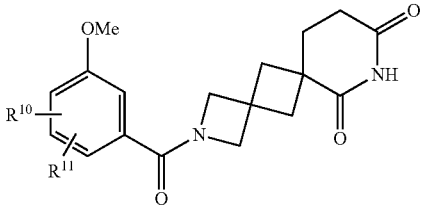

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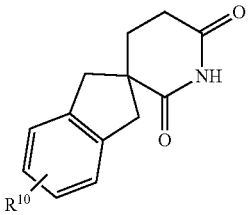

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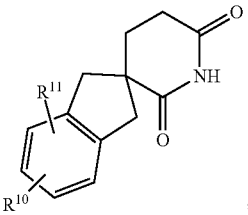

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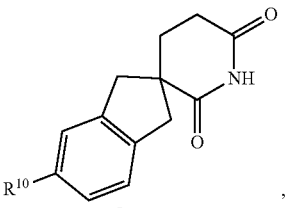

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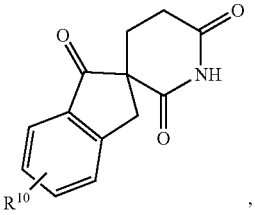

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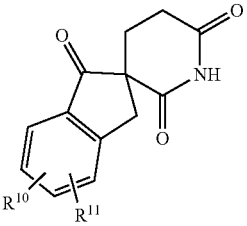

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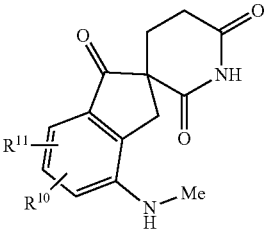

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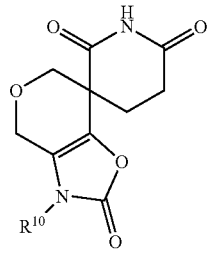

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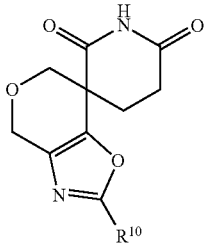

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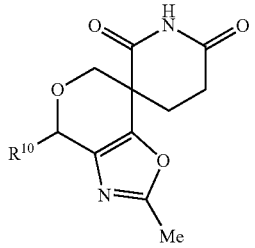

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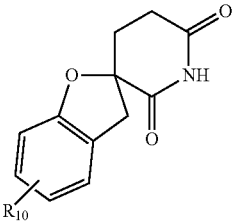

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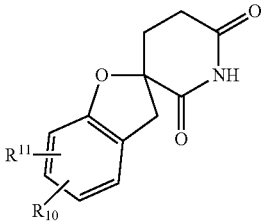

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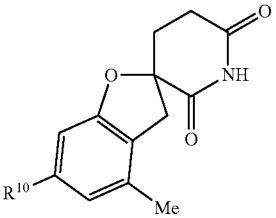

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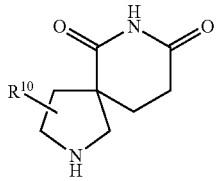

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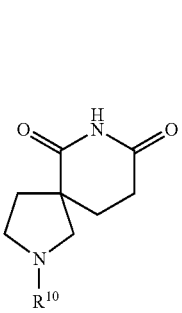

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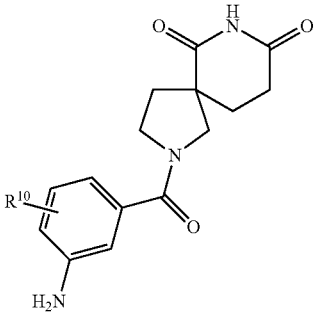

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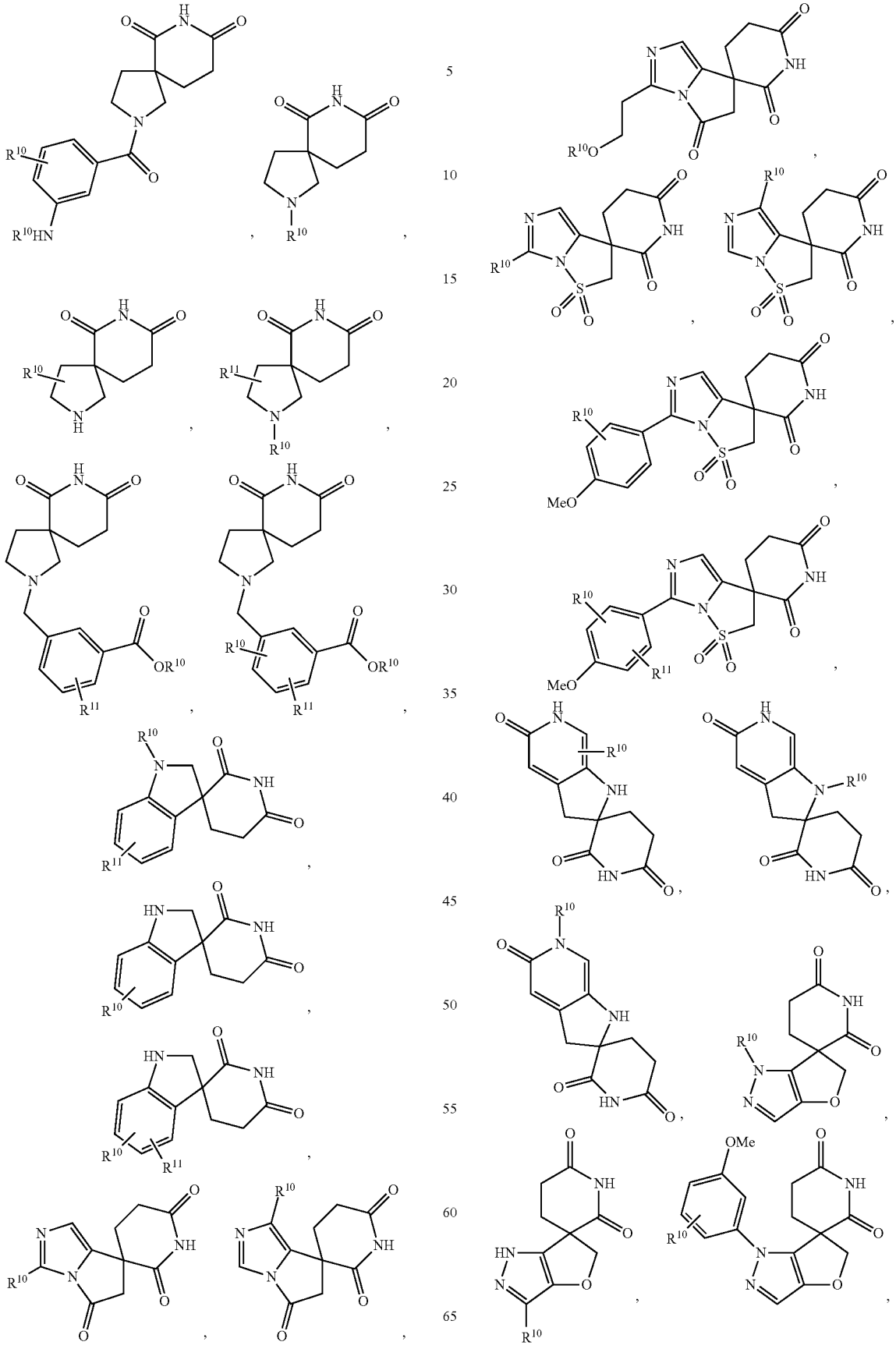

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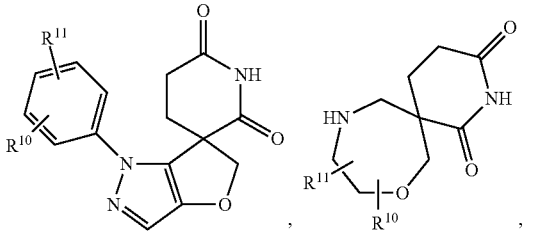
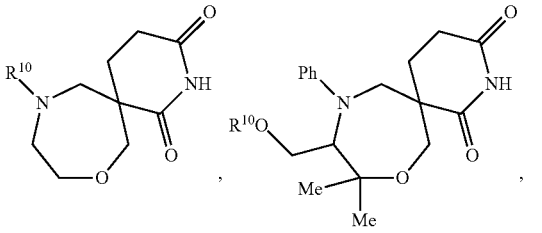
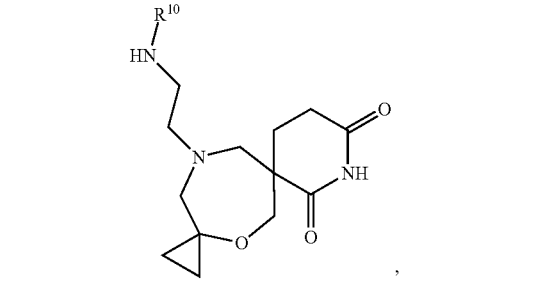
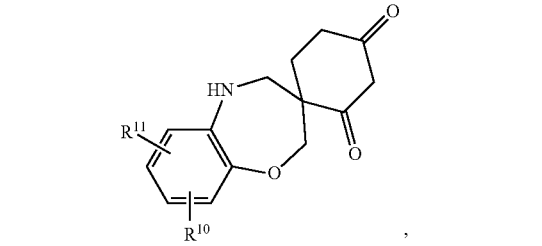
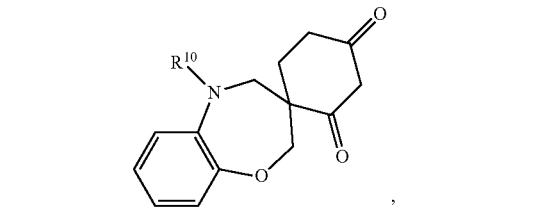
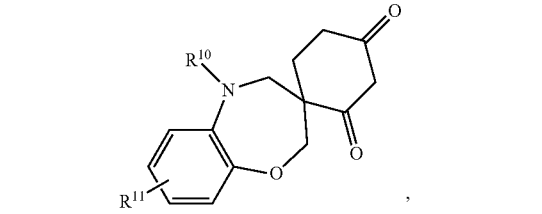




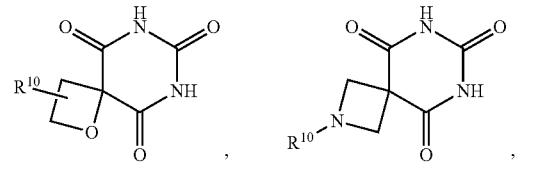








Non-limiting examples of compounds of Formula II include:



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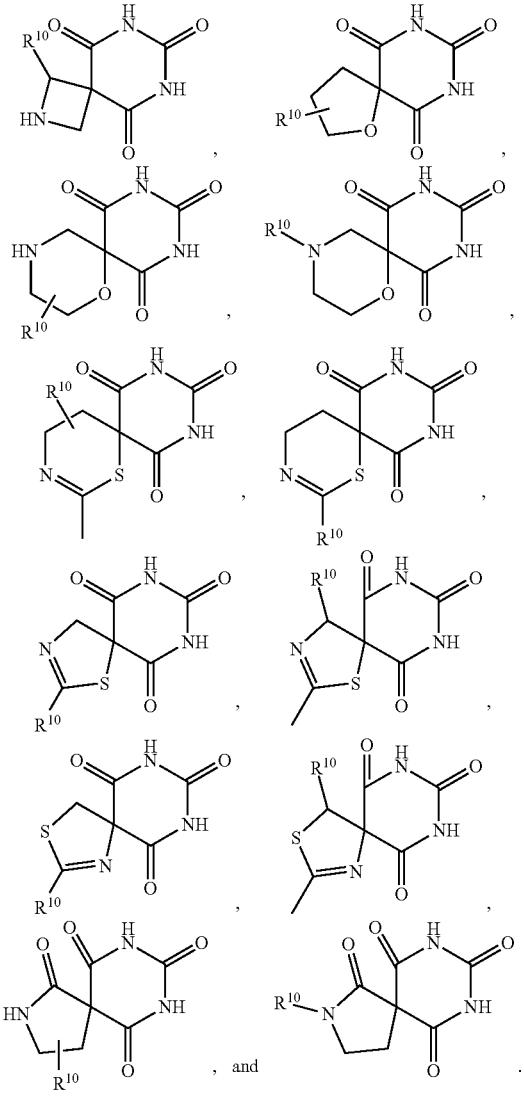

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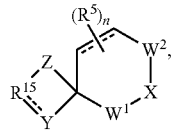
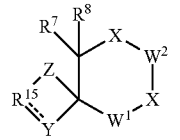
Formula III and Formula IV

In another aspect of the present invention a Degron of Formula III or Formula IV is provided:

(III)



(IV)



or a pharmaceutically acceptable salt, N-oxide, isotopic derivative or prodrug, optionally in a pharmaceutically

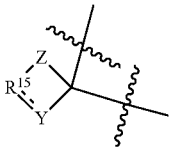
acceptable carrier to create a pharmaceutical composition; wherein the variables are as defined above,

and wherein:

R^{15} is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom as long as the resultant molecule has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable, and wherein the ring atoms are optionally substituted with R^1;

wherein the contiguous atoms of R^{15} can be attached through a single or double bond;

or in an alternative embodiment



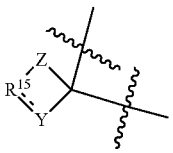
forms a bicyclic moiety which is substituted with R^{10} and optionally substituted with one or more groups independently selected from R^{11} and oxo;

R^{11} is selected at each instance from: hydrogen, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, aryl, heteroaryl, alkylamino, alkylhydroxyl, and haloalkyl;

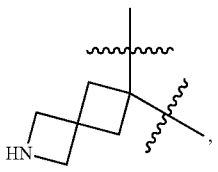
R^{12} is selected from alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)alkyl, —C(O)Oalkyl, —NHalkyl, —N(alkyl)$_2$, —NHSO$_2$alkyl, —N(alkyl)SO$_2$alkyl, —NHSO$_2$aryl, —N(alkyl)SO$_2$aryl, —NHSO$_2$alkenyl, —N(alkyl)SO$_2$alkenyl, —NHSO$_2$alkynyl, —N(alkyl)SO$_2$alkynyl, cyano, nitro, nitroso, —SH,-Salkyl, and haloalkyl; and

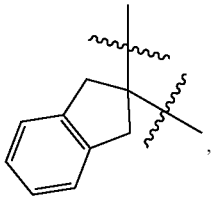
R^{13} is selected from alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, —C(O)Oalkyl.

Non-limiting examples of bicyclic



moieties include:





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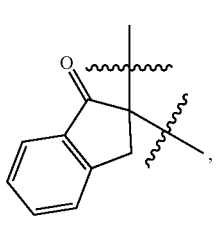

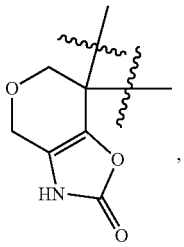

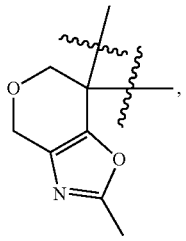

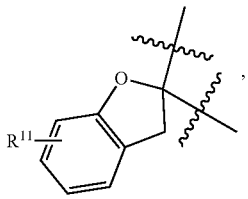

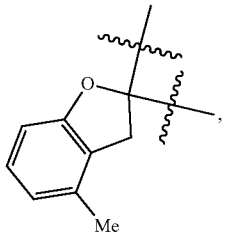

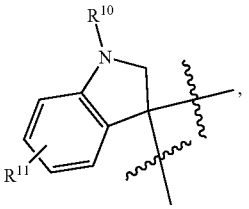

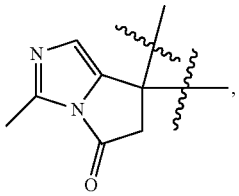

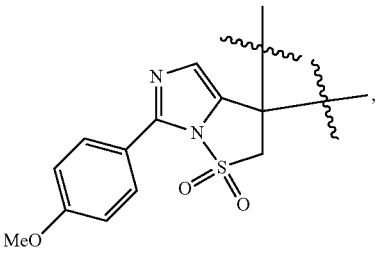

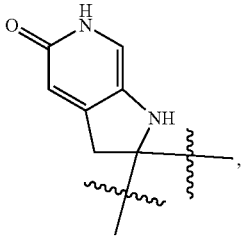

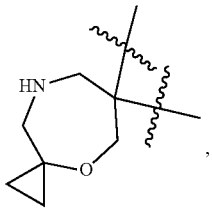

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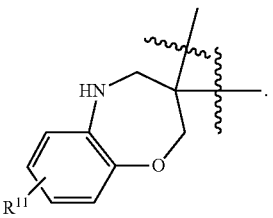
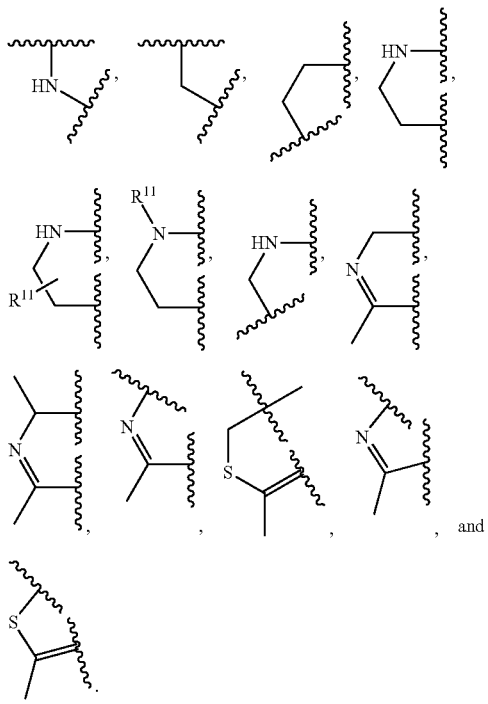
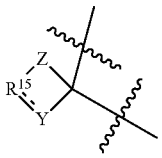


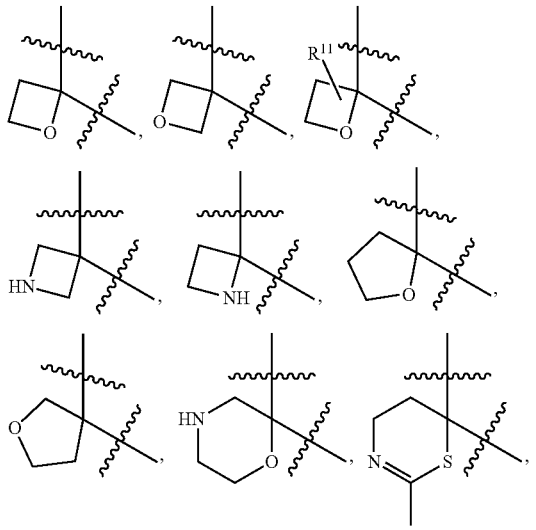
Non-limiting examples of R^{15} include:



Non-limiting examples of



include:



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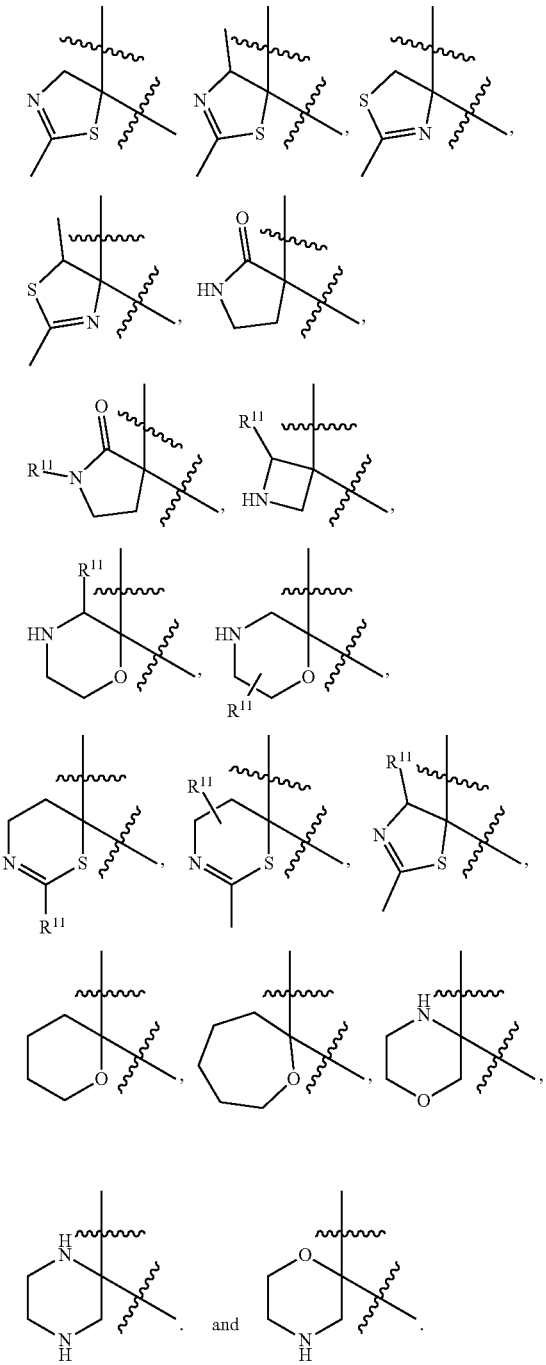
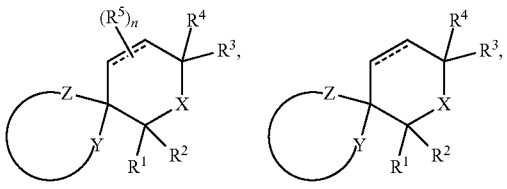


Additional non limiting examples of compounds of Formula III include:



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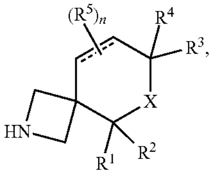
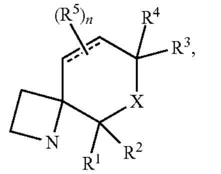
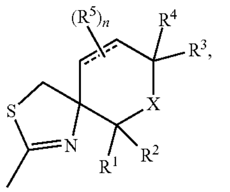
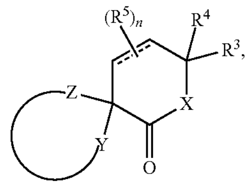
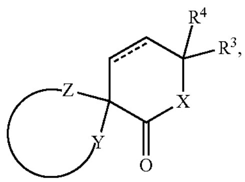
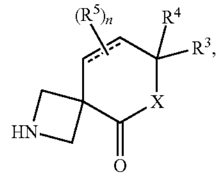
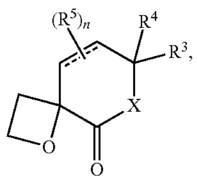
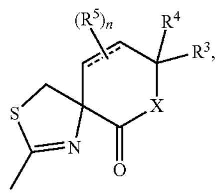
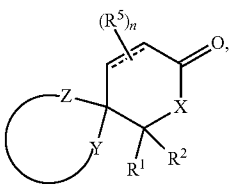
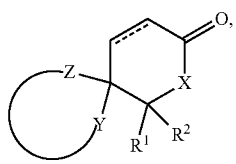
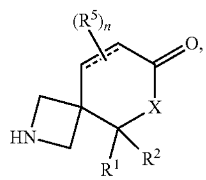
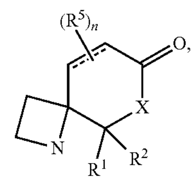
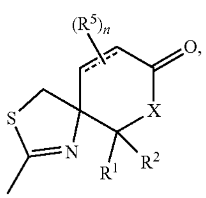
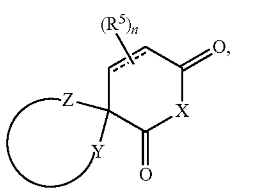
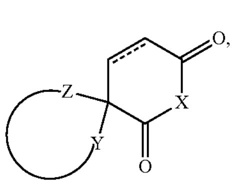
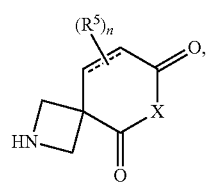
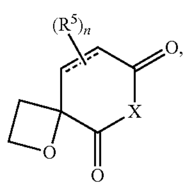
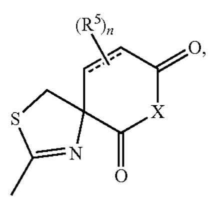

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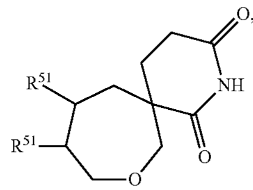
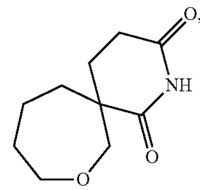
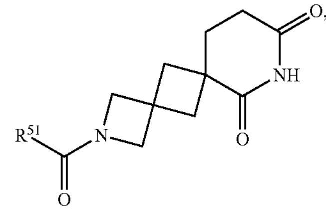
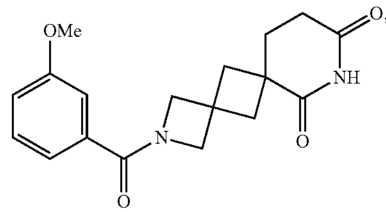
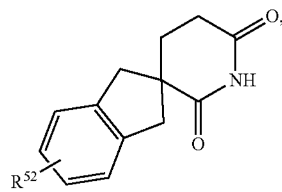
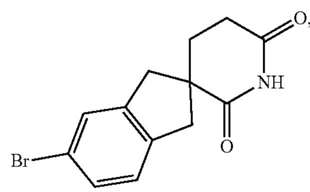
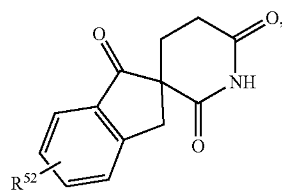
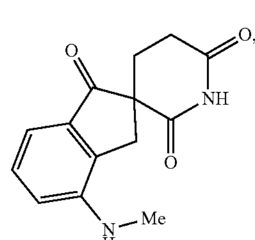
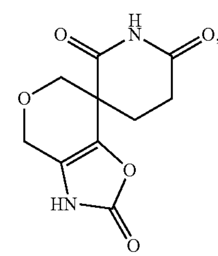
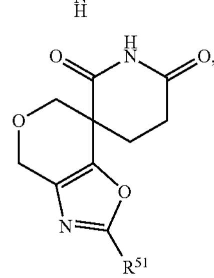
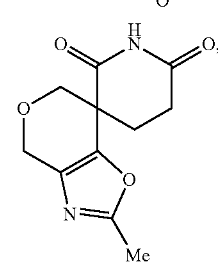

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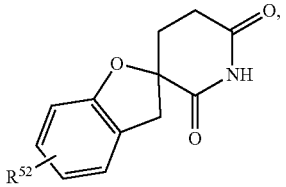

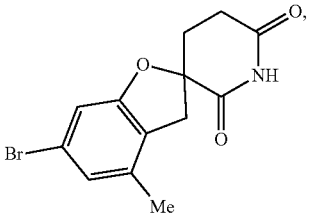

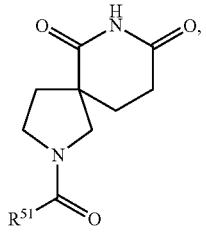

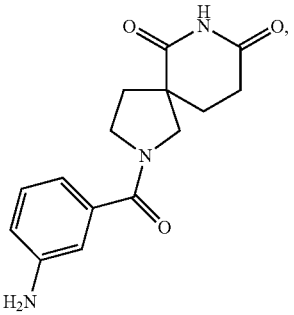

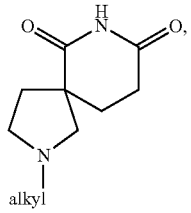

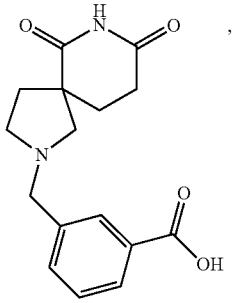

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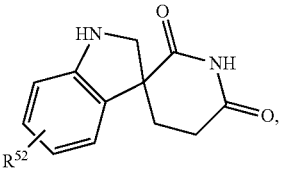

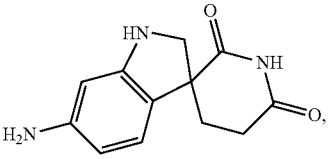

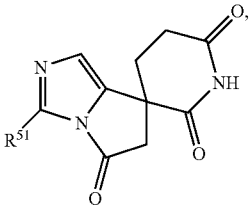

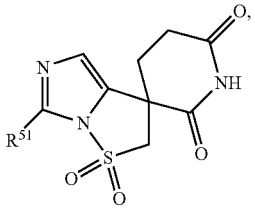

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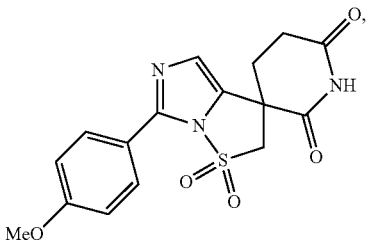

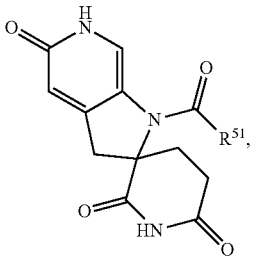

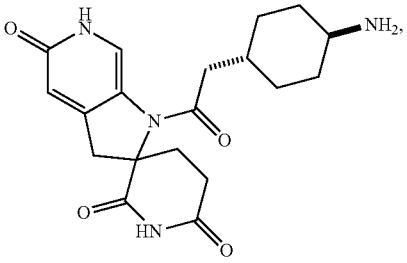

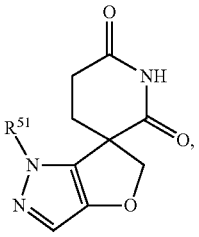

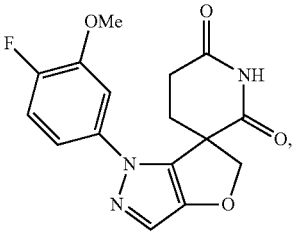

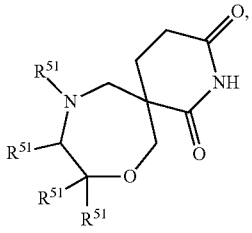

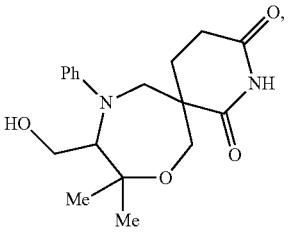

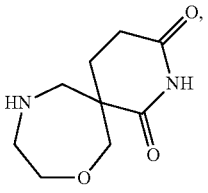

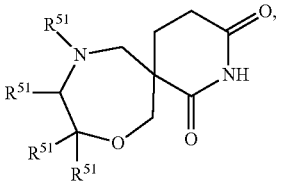

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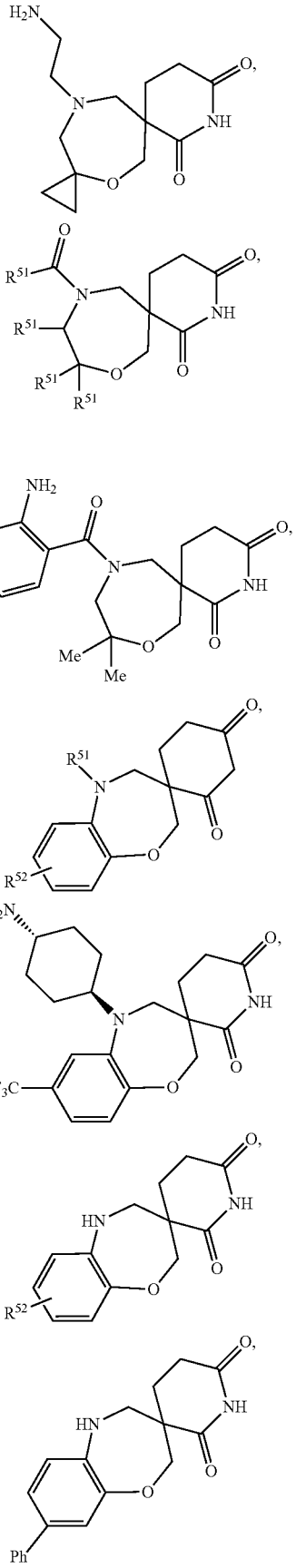

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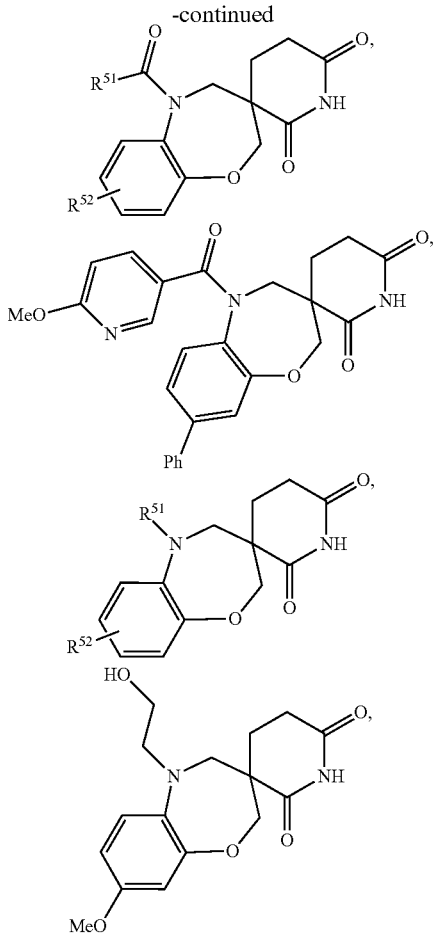


wherein, ◯ represents 0 to 5 contiguous atoms attached to both Y and Z to form a 3, 4, 5, 6, 7, or 8-membered ring;

R^{51} is independently selected from —H, alkyl, aryl, heteroaryl; and

R^{52} is independently selected from —H, —F, —Cl, —Br, alkyl, aryl, heteroaryl, —OH, —OMe, —NHMe, —NH_2.

Linker

A Linker is included in the Degronimers of Formula I and II. Linker is a bond or a chemically stable group that attaches a Degron to a Targeting Ligand.

Any of the Linkers described herein can be used in either direction, i.e., either the left end is linked to the Degron and the right end to the Target Linker, or the left end is linked to the Target Linker and the right end is linked to the Degron. According to the invention, any desired linker can be used as long as the resulting compound has a stable shelf life for at least 2 months, 3 months, 6 months or 1 year as part of a pharmaceutically acceptable dosage form, and itself is pharmaceutically acceptable.

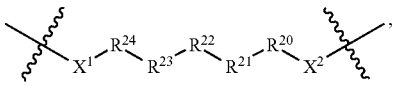
In a typical embodiment, the Linker has a chain of 2 to 14, 15, 16, 17, 18 or 20 or more carbon atoms of which one or more carbons can be replaced by a heteroatom such as O, N, S, or P. In certain embodiments the chain has 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous atoms in the chain. For example, the chain may include 1 or more ethylene glycol units that can be contiguous, partially contiguous or non-contiguous (for example, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ethylene glycol units). In certain embodi-

ments, the chain has at least 1, 2, 3, 4, 5, 6, 7, or 8 contiguous chains which can have branches which can be independently alkyl, heteroalkyl, aryl, heteroaryl, alkenyl, or alkynyl, aliphatic, heteroaliphatic, cycloalkyl or heterocyclic substituents.

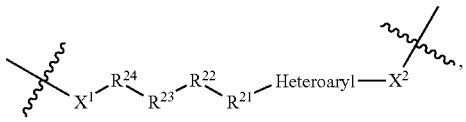
In other embodiments, the linker can include or be comprised of one or more of ethylene glycol, propylene glycol, lactic acid and/or glycolic acid. In general, propylene glycol adds hydrophobicity, while propylene glycol adds hydrophilicity. Lactic acid segments tend to have a longer half-life than glycolic acid segments. Block and random lactic acid-co-glycolic acid moieties, as well as ethylene glycol and propylene glycol, are known in the art to be pharmaceutically acceptable and can be modified or arranged to obtain the desired half-life and hydrophilicity. In certain aspects, these units can be flanked or interspersed with other moieties, such as aliphatic, including alkyl, heteroaliphatic, aryl, heteroaryl, heterocyclic, cycloalkyl, etc., as desired to achieve the appropriate drug properties.

In one embodiment, the Linker is a moiety selected from Formula LI, Formula LII, Formula LIII, Formula LIV, Formula LV, Formula LVI, and Formula LVII:

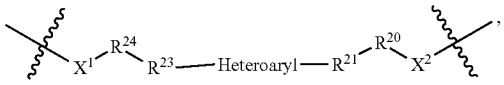
(LI)



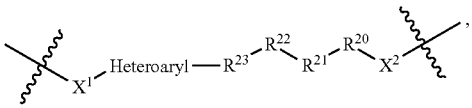
(LII)



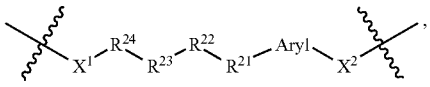
(LIII)



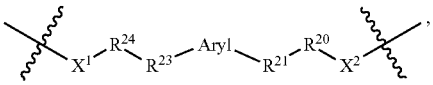
(LIV)



(LV)

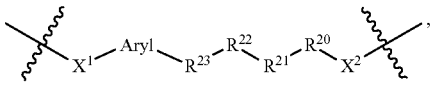


(LVI)



and

(LVII)



wherein:

X^1 and X^2 are independently selected from bond, NH, NR^{25}, CH_2, CHR^{25}, $C(R^{25})_2$, O, and S;

R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from bond, alkyl, —C(O)— —C(O)O—, —OC(O)—, —C(O)alkyl, —C(O)Oalkyl, —C(S)—, —SO_2—, —S(O)—, —C(S)—, —C(O)NH—, —NHC(O)—, —N(alkyl)C(O)—, —C(O)N(alkyl)-, —O—, —S—, —NH—, —N(alkyl)-, —CH(—O—R^{26})—, —CH(—NHR^{25})—, —CH(—NH_2)—, —CH(—$NR^{25}{}_2$)—, —C(—O—R^{26})alkyl-, —C(—NHR^{25})alkyl-, —C(—NH_2)alkyl-, —C(—$NR^{25}{}_2$)alkyl-, —C(R^4R^4)—, -alkyl(R^{27})-alkyl(R^{28})—, —C($R^{27}R^{28}$)—, —P(O)(OR^{26})O—, —P(O)(OR^{26})—, —NHC(O)NH—, —N(R^{25})C(O)N(R^{25})—, —N(H)C(O)N(R^{25})—, polyethylene glycol, poly(lactic-co-glycolic acid), alkene, haloalkyl, alkoxy, and alkyne;

or R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} can in addition to those above be independently selected from heteroarylalkyl, aryl, arylalkyl, heterocycle, aliphatic, heteroaliphatic, heteroaryl, polypropylene glycol, lactic acid, glycolic acid, carbocycle, or —O—$(CH_2)_{1\text{-}12}$—O—, —NH—$(CH_2)_{1\text{-}12}$—NH—, —NH—$(CH_2)_{1\text{-}12}$—O—, or —O—$(CH_2)_{1\text{-}12}$—NH—, —S—$(CH_2)_{1\text{-}12}$—O—, —O—$(CH_2)_{1\text{-}12}$—S—, —S—$(CH_2)_{1\text{-}12}$—S—, —S—$(CH_2)_{1\text{-}12}$—NH—, —NH—$(CH_2)_{1\text{-}12}$—S—, (and wherein the 1-12 can be independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, and wherein one or more of the CH_2 or NH can be modified by substitution of a H for a methyl, ethyl, cyclopropyl, F (if on carbon), etc, as described herein), and optionally, a heteroatom, heteroalkyl, aryl, heteroaryl or cycloaliphatic group is interspersed in the chain). Certain nonlimiting examples include —O—CH(CH_3)—CH(CH_3)CH—O—, —O—CH_2—CH(CH_3)CH—O—, —O—CH(CH_3)—CH_2CH—O—, etc.

each of which R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} is optionally substituted with one or more substituents selected from R^{101} or alternatively as described in Section 1. Definitions;

R^{25} is selected at each instance from: alkyl, —C(O)H, —C(O)OH, —C(O)alkyl, —C(O)Oalkyl, alkenyl, or alkynyl or alternatively can be aliphatic, heteroaliphatic, aryl, heteroaryl or heterocyclic;

R^{26} is hydrogen, alkyl, silane, arylalkyl, heteroarylalkyl, alkene, and alkyne; or in addition to these can also be selected from aryl, heteroaryl, heterocyclic, aliphatic and heteroaliphatic;

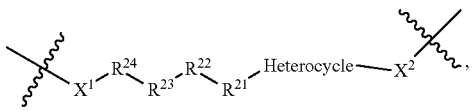
R^{27} and R^{28} are independently selected from hydrogen, alkyl, amine, or together with the carbon atom to which they are attached, form C(O), C(S), C=CH_2, a C_3-C_6 spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O, or form a 1 or 2 carbon bridged ring;

R^{101} is independently selected at each occurrence from hydrogen, alkyl, alkene, alkyne, haloalkyl, alkoxy, hydroxyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocycloalkyl, aryloxy, heteroaryloxy, CN, —COOalkyl, COOH, NO_2, F, Cl, Br, I, CF_3, NH_2, NHalkyl, N(alkyl)$_2$, $NR^{25}R^{25}$, NHR^{25}, aliphatic, heteroaliphatic, and COR^4; and

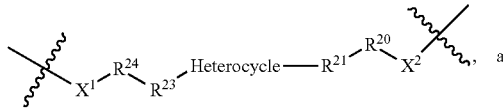
R^4 is selected from hydrogen, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclic, hydroxyl, alkoxy, amine, —NHalkyl, or —Nalkyl$_2$;

In an additional embodiment, the Linker is a moiety selected from Formula LVIII, LIX, and LX:

(LVIII)



(LIX)



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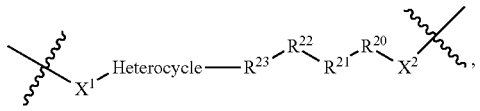
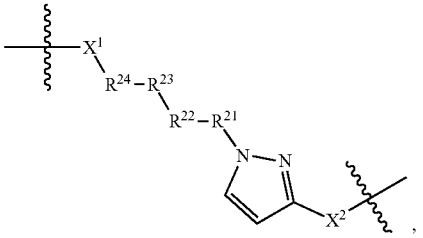
(LX)

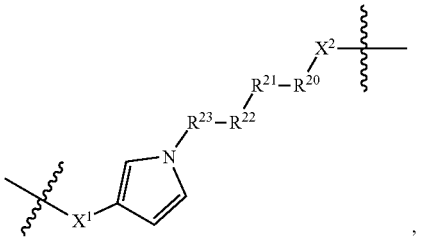


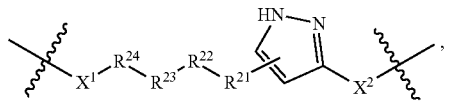
wherein each variable is as it is defined in Formula LI. In alternative embodiments of LVIII, LIX and LX, a carbocyclic ring is used in place of the heterocycle.

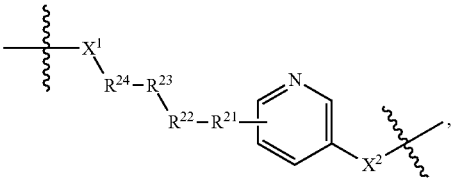
The following are non-limiting examples of Linkers that can be used in this invention. Based on this elaboration, those of skill in the art will understand how to use the full breadth of Linkers that will accomplish the goal of the invention.

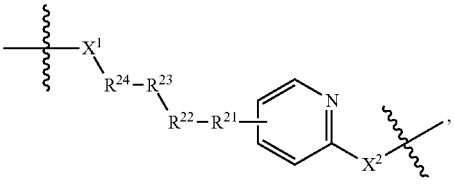
As certain non-limiting examples, Formula LI, Formula LII, Formula LIII, Formula LIV, Formula LV, Formula LVI, or Formula LVII include:

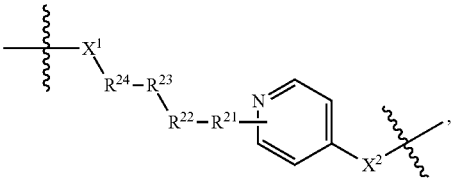












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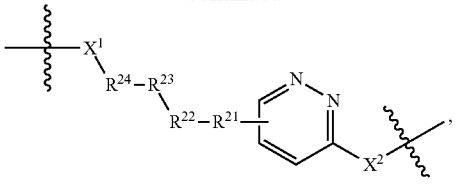

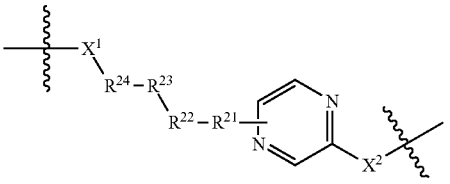

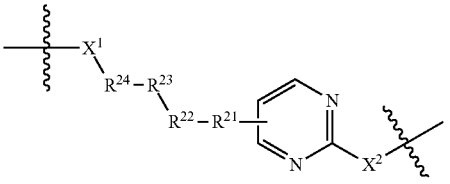

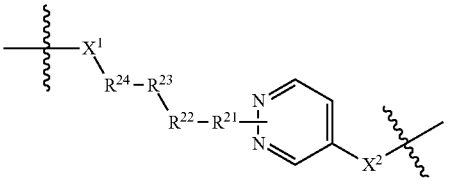

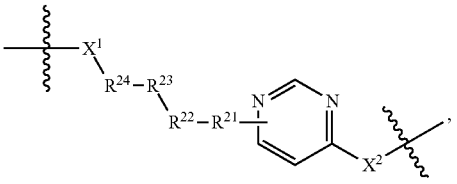

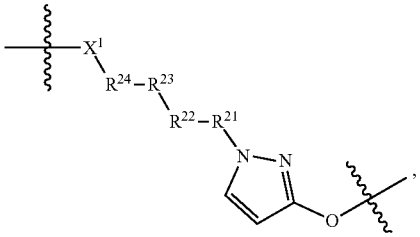

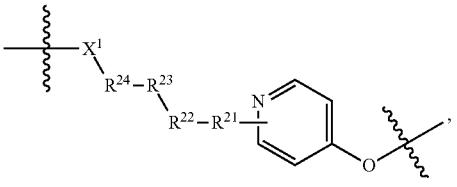

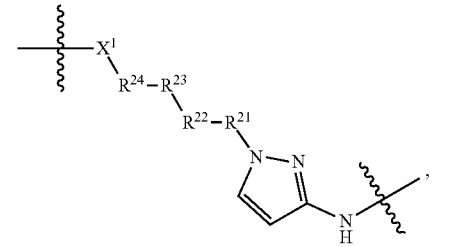

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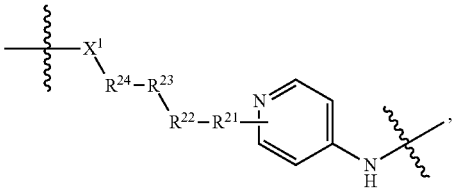

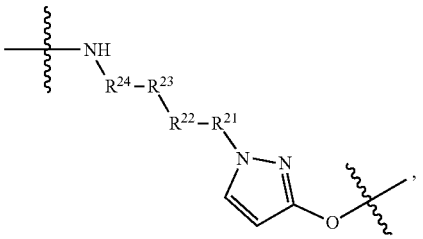

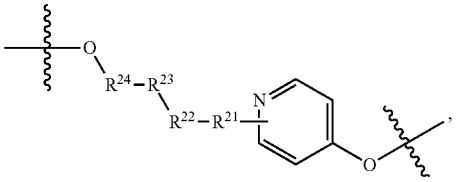

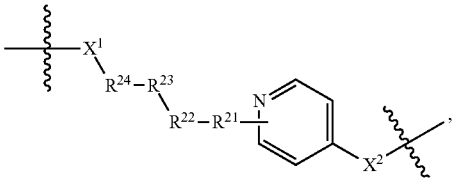

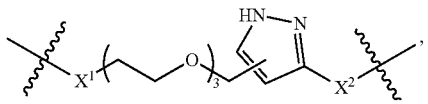

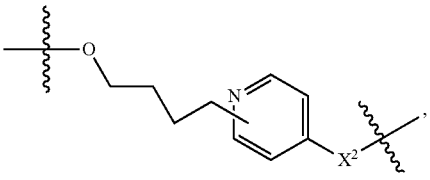

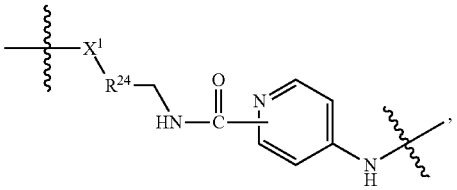

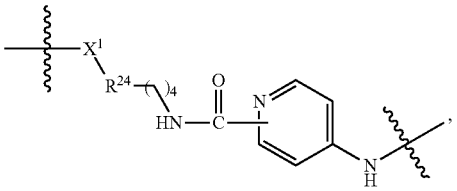

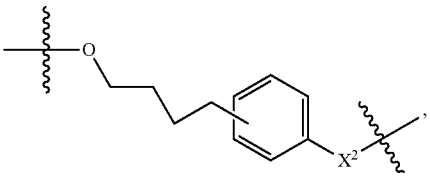

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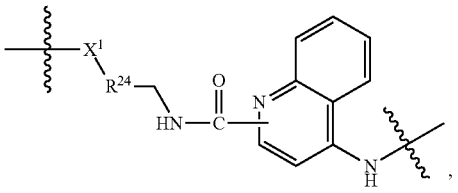

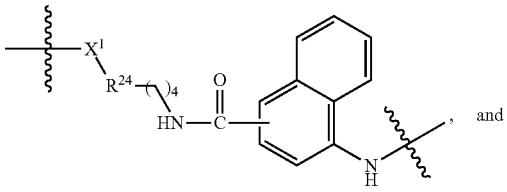

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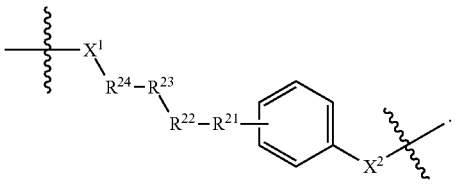
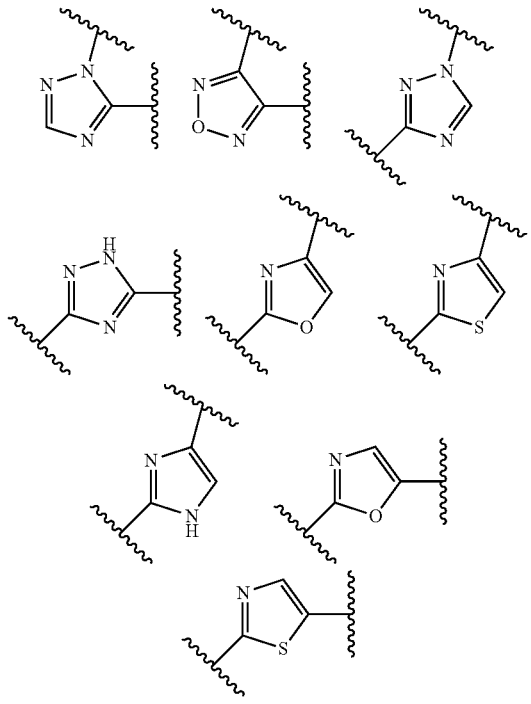
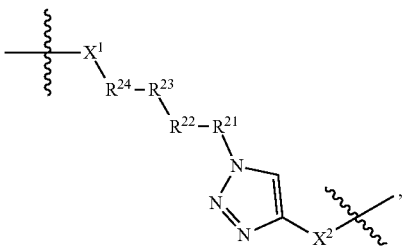


In an additional embodiment Linker is selected from:



In an additional embodiment Linker is selected from:



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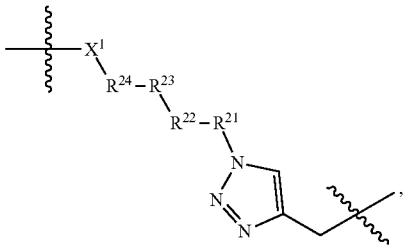

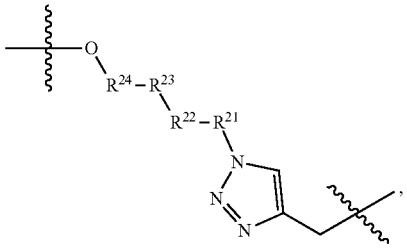

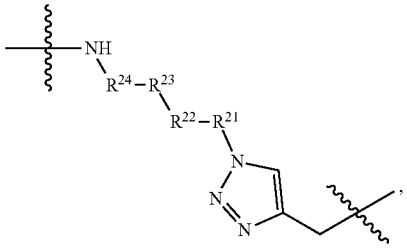

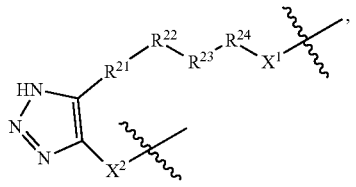

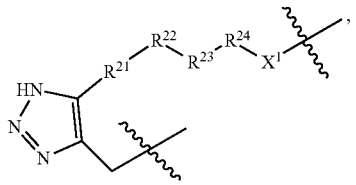

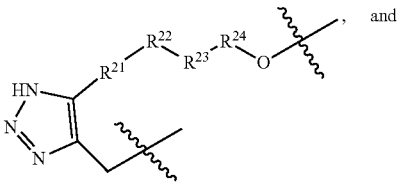

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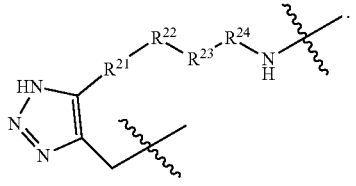
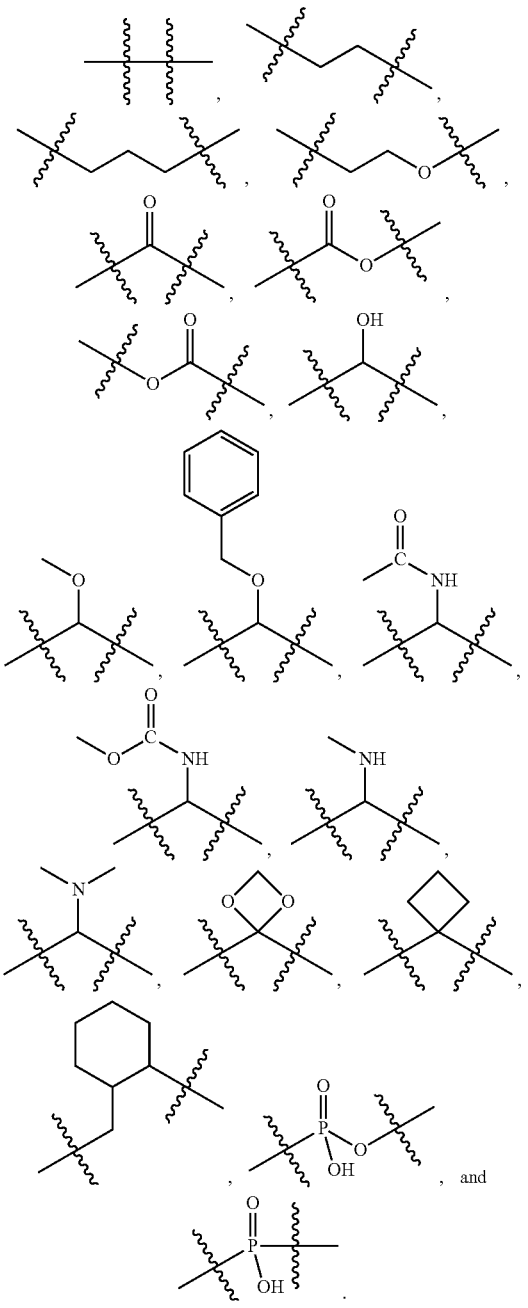


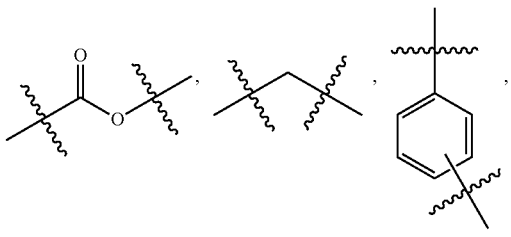
In one embodiment X^1 is attached to the Targeting Ligand. In another embodiment X^2 is attached to the Targeting Ligand.

Non-limiting examples of moieties of R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} include:



and

Additional non-limiting examples of moieties of R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} include:



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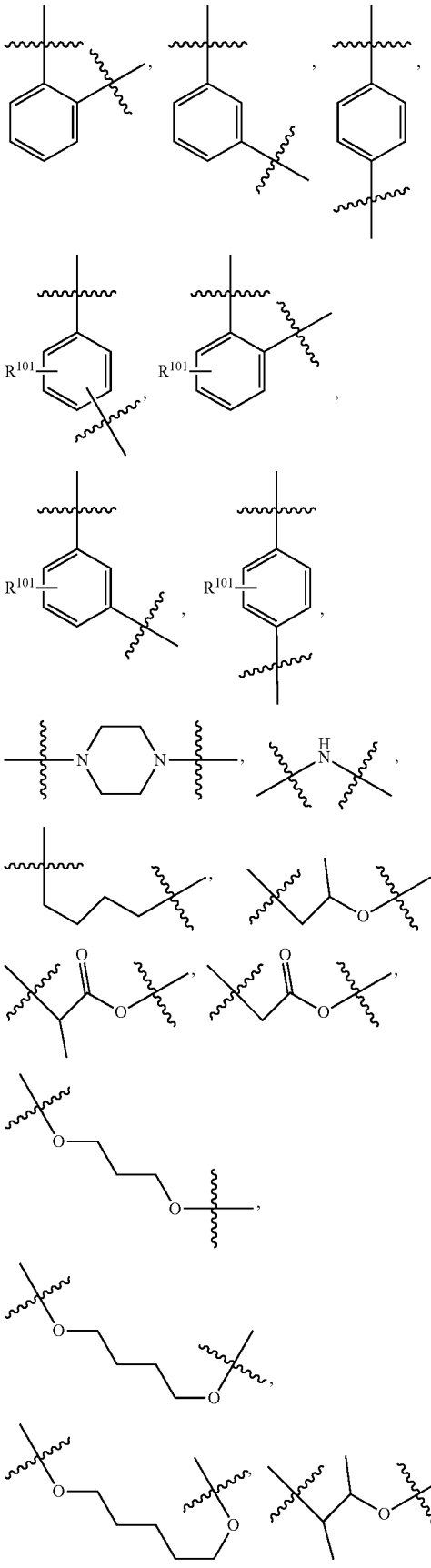

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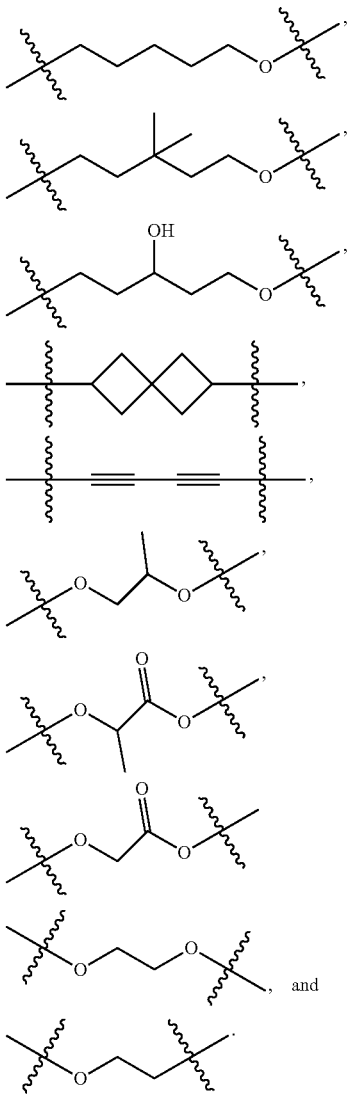
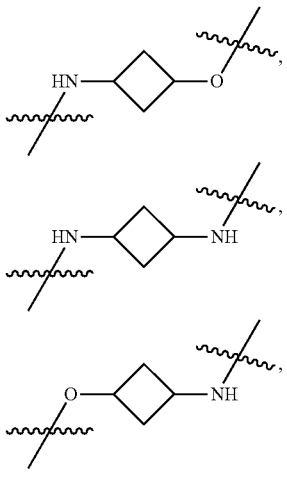


and

Additional non-limiting examples of moieties of R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} include:



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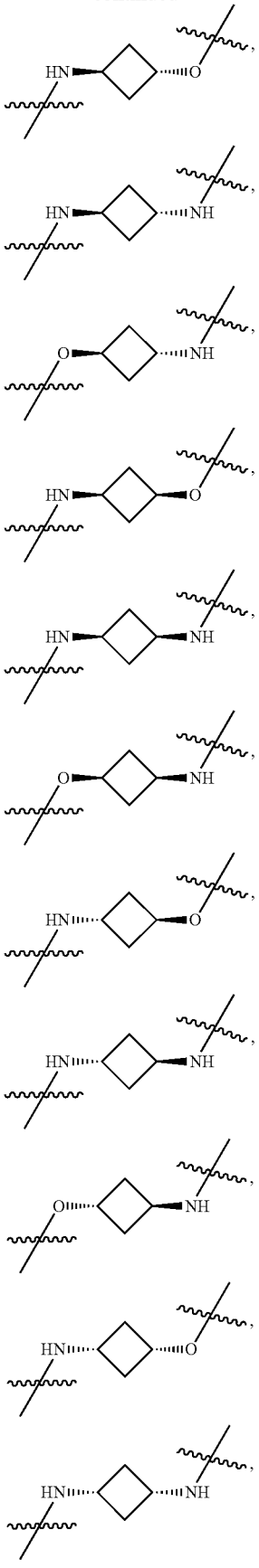

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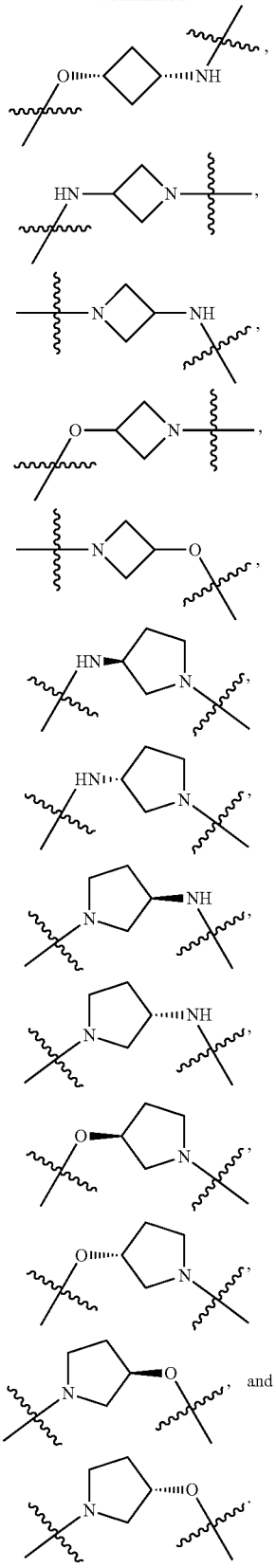


and

In additional embodiments, the Linker group is an optionally substituted (poly)ethylene glycol having at least 1, at

least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, ethylene glycol units, or optionally substituted alkyl groups interspersed with optionally substituted, O, N, S, P or Si atoms. In certain embodiments, the Linker is flanked, substituted, or interspersed with an aryl, phenyl, benzyl, alkyl, alkylene, or heterocycle group. In certain embodiments, the Linker may be asymmetric or symmetrical. In some embodiments, the Linker is a substituted or unsubstituted polyethylene glycol group ranging in size from about 1 to about 12 ethylene glycol units, between 1 and about 10 ethylene glycol units, about 2 about 6 ethylene glycol units, between about 2 and 5 ethylene glycol units, between about 2 and 4 ethylene glycol units. In any of the embodiments of the compounds described herein, the Linker group may be any suitable moiety as described herein.

In additional embodiments, the Linker is selected from: —$NR^{61}(CH_2)_{n1}$-(lower alkyl)-, —$NR^{61}(CH_2)_{n1}$-(lower alkoxyl)-, —$NR^{61}(CH_2)_{n1}$-(lower alkoxyl)-OCH_2—, —$NR^{61}(CH_2)_{n1}$-(lower alkoxyl)-(lower alkyl)-OCH_2—, —$NR^{61}(CH_2)_{n1}$-(cycloalkyl)-(lower alkyl)-OCH_2—, —$NR^{61}(CH_2)_{n1}$-(heterocycloalkyl)-, —$NR^{61}(CH_2CH_2O)_{n1}$-(lower alkyl)-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(heterocycloalkyl)-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-Aryl-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(heteroaryl)-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(cycloalkyl)-O-(heteroaryl)-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(cycloalkyl)-O-Aryl-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(lower alkyl)-NH-Aryl-O—CH_2—, —$NR^{61}(CH_2CH_2O)_{n1}$-(lower alkyl)-O-Aryl-CH_2, —$NR^{61}(CH_2CH_2O)$n-cycloalkyl-O-Aryl-, —$NR^{61}(CH_2CH_2O)_{n1}$-cycloalkyl-O-heteroaryl-, —$NR^{61}(CH_2CH_2)_{n1}$-(cycloalkyl)-O-(heterocycle)-CH_2, —$NR^{61}(CH_2CH_2)_{n1}$-(heterocycle)-(heterocycle)-CH_2, and —NR^{61}-(heterocycle)-CH_2;

wherein n1 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

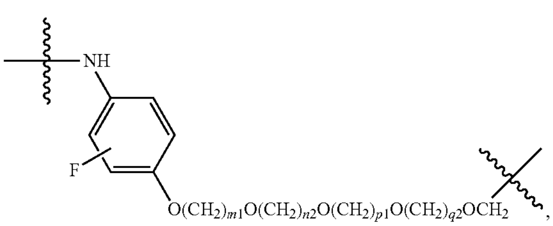
R^{61} is H, methyl, or ethyl.

In additional embodiments, the Linker is selected from: —$N(R^{61})$—$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—OCH_2—; —O—$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—OCH_2—, —O—$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—O—; —$N(R^{61})$—$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—O—; —$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—O—; —$(CH_2)_{m1}$—$O(CH_2)_{n2}$—$O(CH_2)_{o1}$—$O(CH_2)_{p1}$—$O(CH_2)_{q1}$—$O(CH_2)_{r1}$—OCH_2—; —$O(CH_2)_{m1}O(CH_2)_{n2}O(CH_2)_{p1}O(CH_2)_{q1}OCH_2$—; —$O(CH_2)_{m1}O(CH_2)_{n2}O(CH_2)_{p1}O(CH_2)_{q1}OCH_2$—; wherein

m1, n2, o1, p1, q1, and r1 are independently 1, 2, 3, 4, or 5; and

R^{61} is H, methyl, or ethyl.

In additional embodiments, the Linker is selected from:



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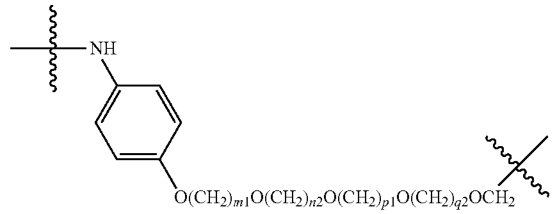

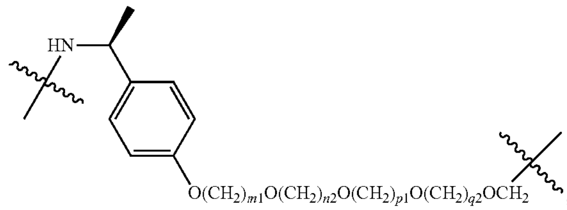

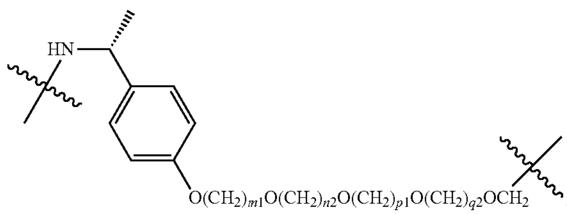

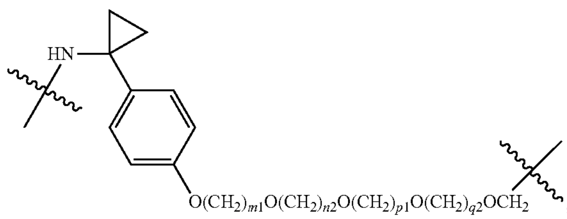

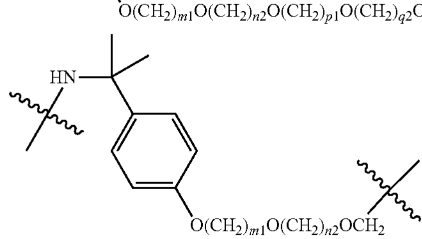

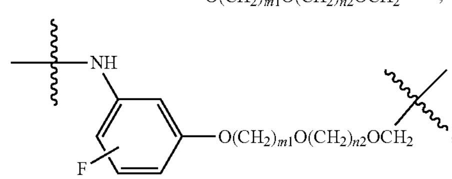

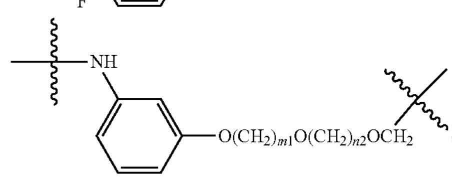

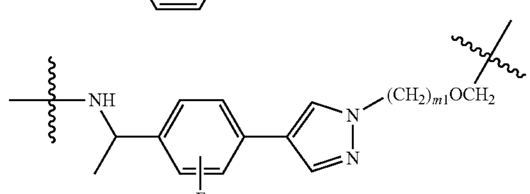

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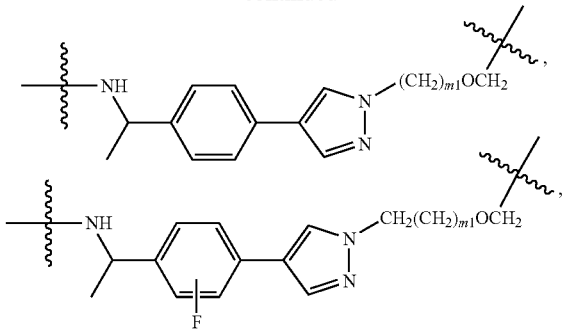

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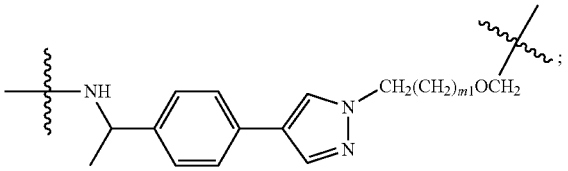
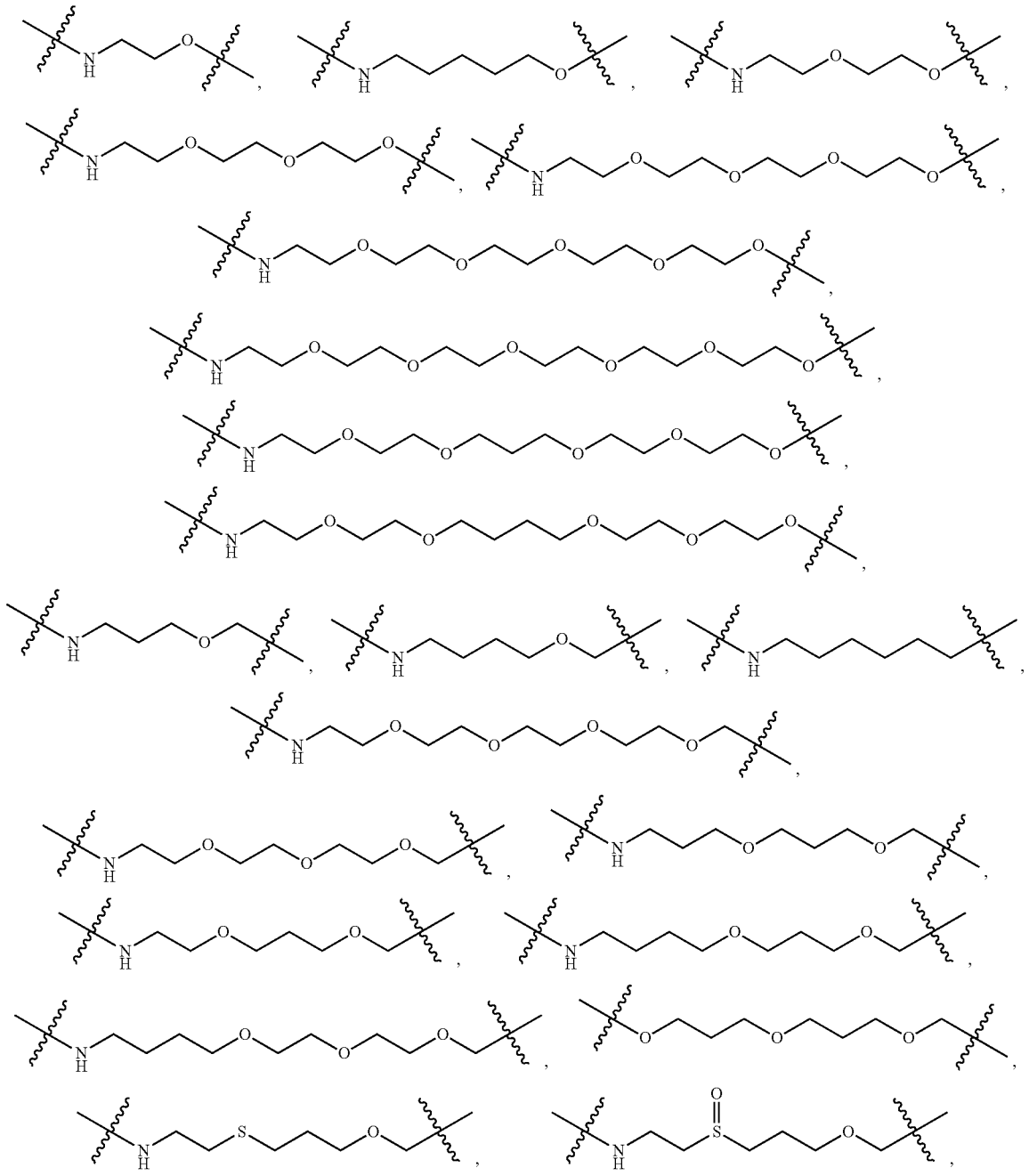


m1, n2, o1, p1, q2, and r1 are independently 1, 2, 3, 4, or 5.

In additional embodiments, the Linker is selected from:



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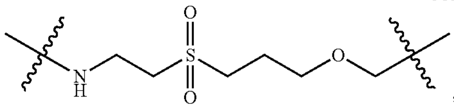
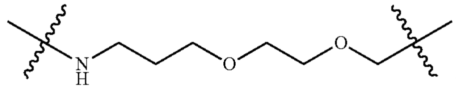
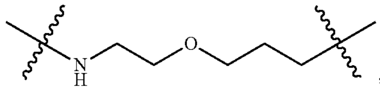
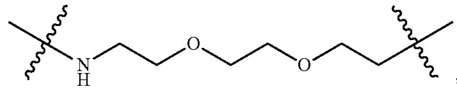
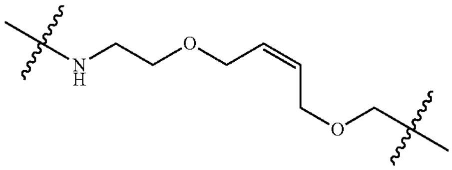
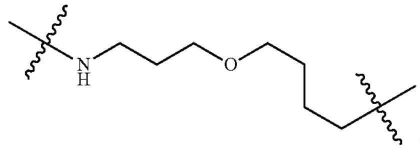
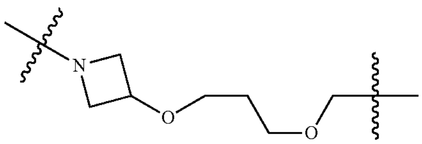
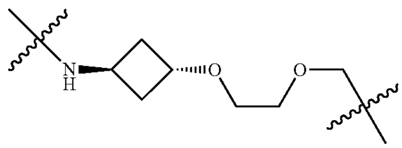
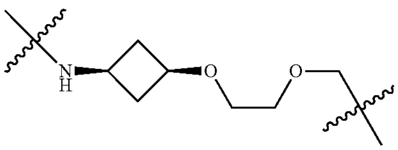
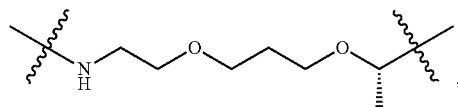
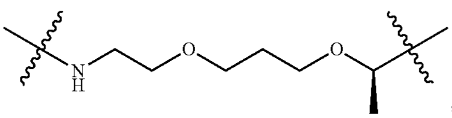
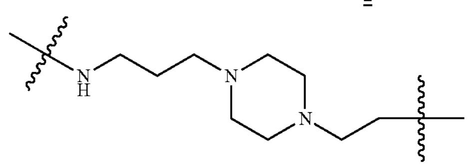
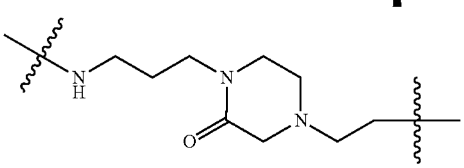
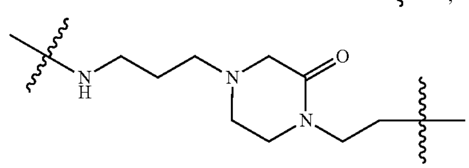
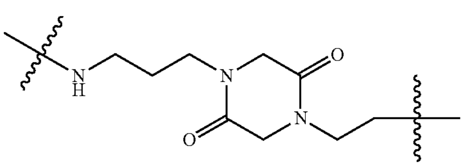
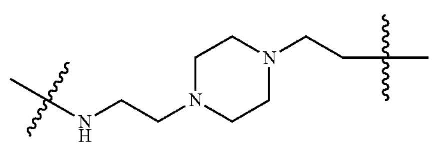
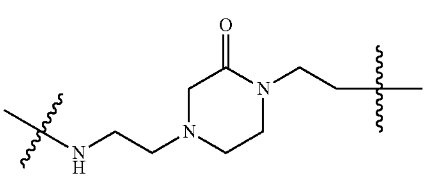
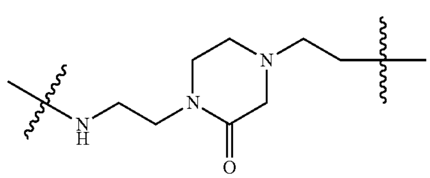
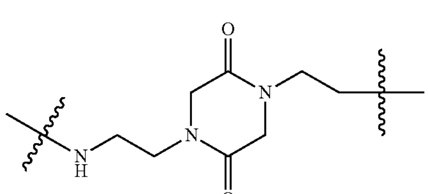
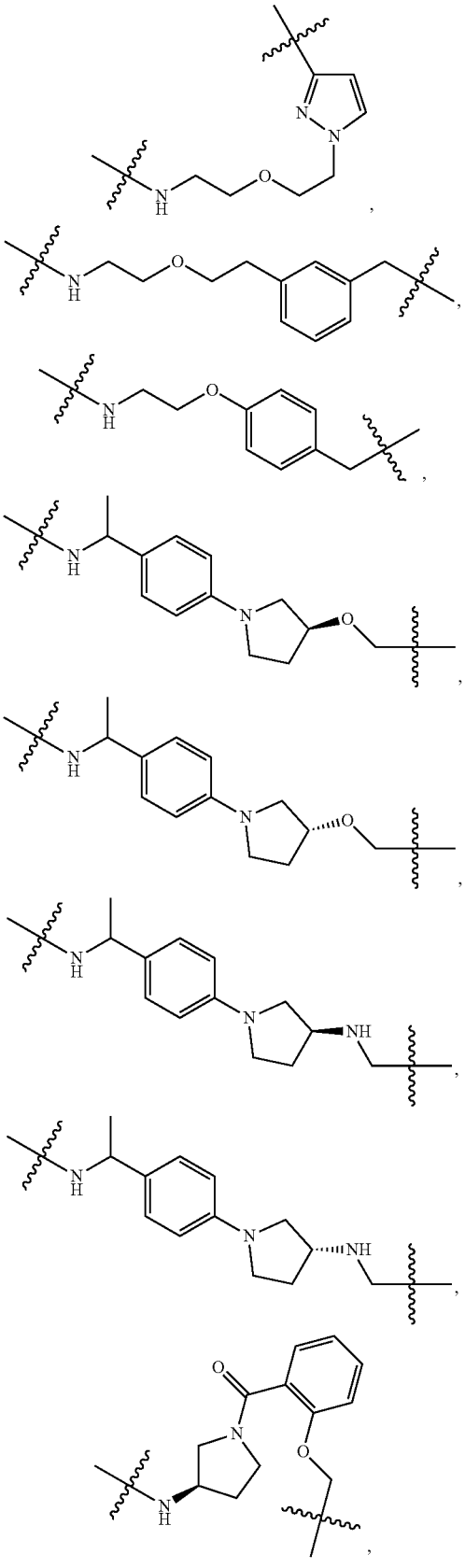
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,


In additional embodiments, the Linker is selected from:



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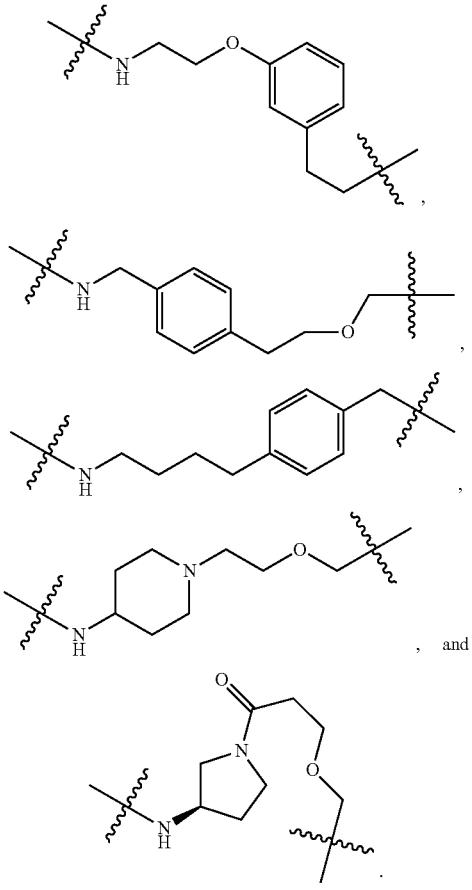
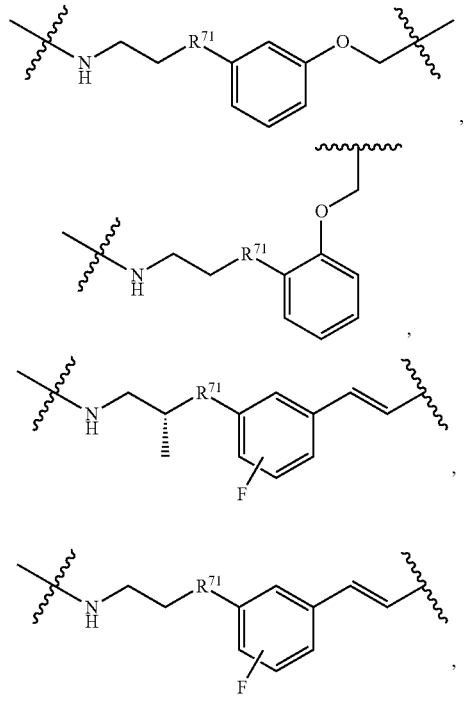


In additional embodiments, the Linker is selected from:



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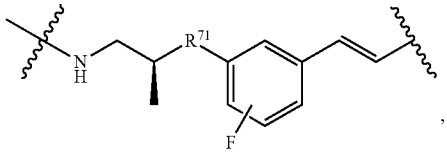

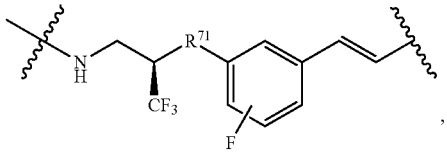

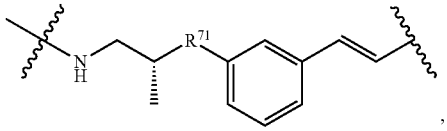

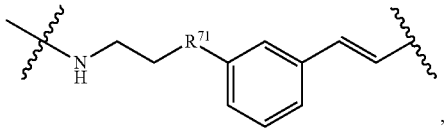

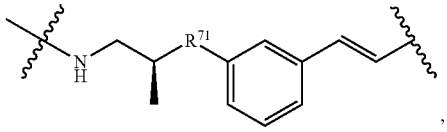

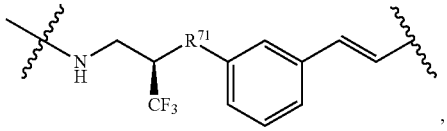

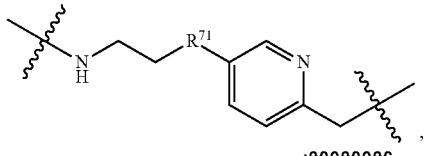

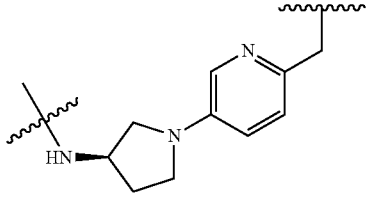

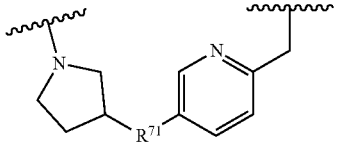

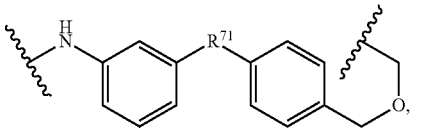

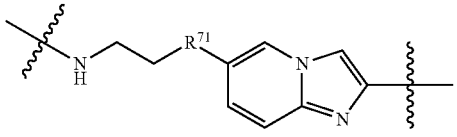

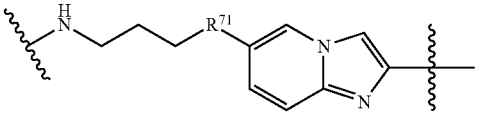

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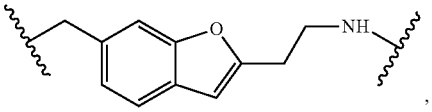

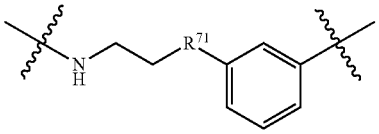

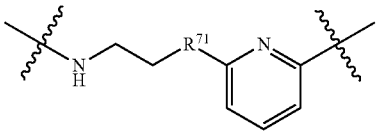

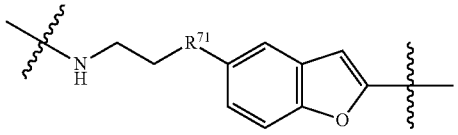

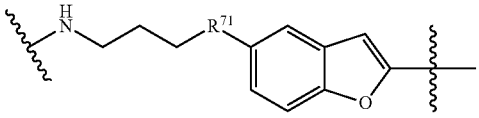

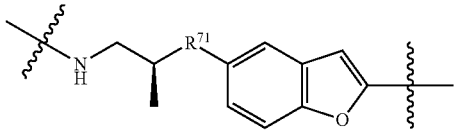

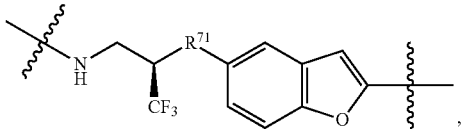

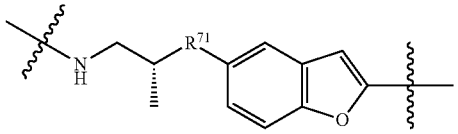

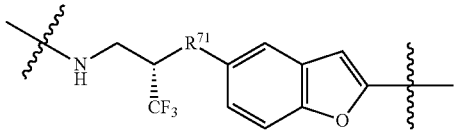

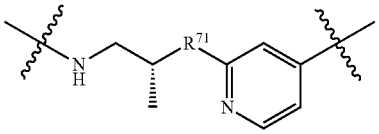

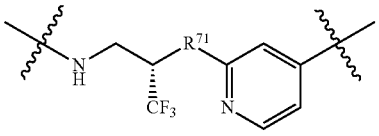

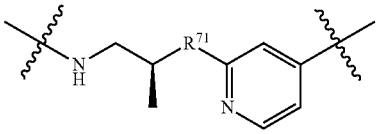

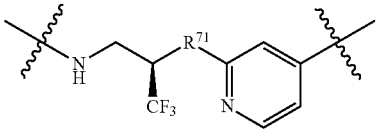

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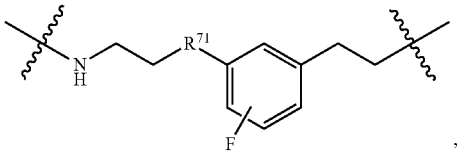

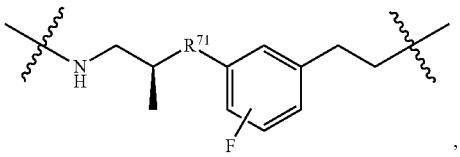

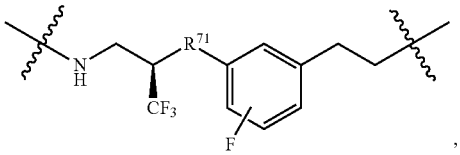

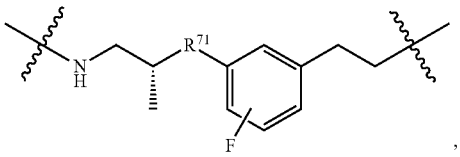

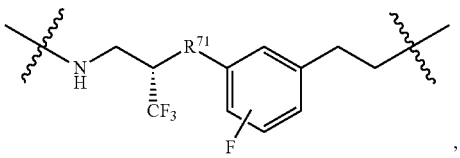

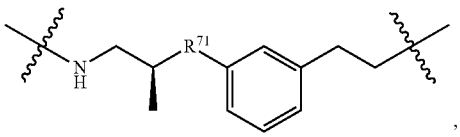

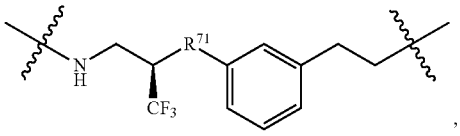

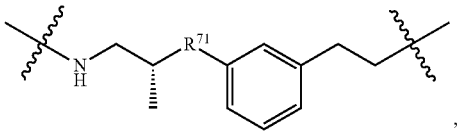

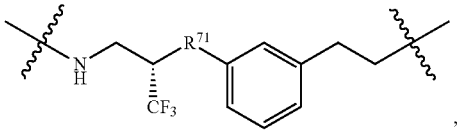

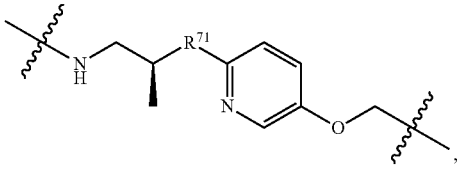

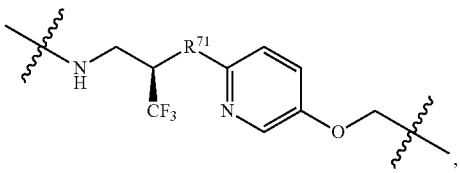

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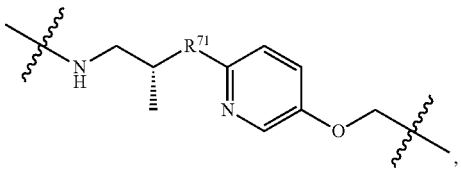

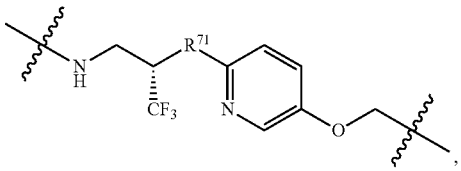

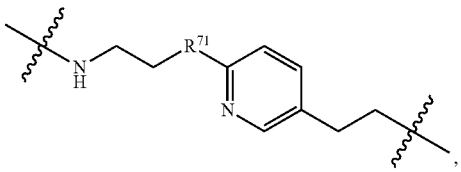

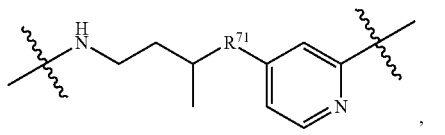

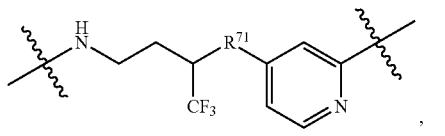

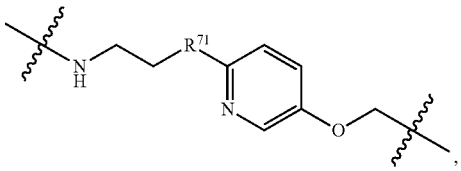

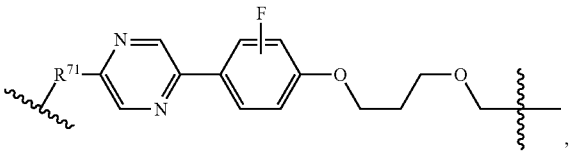

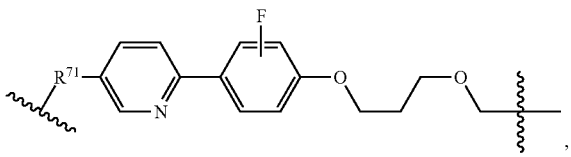

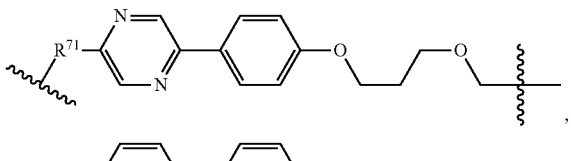

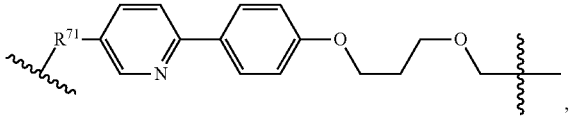

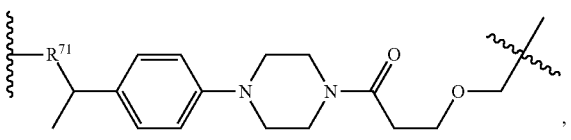

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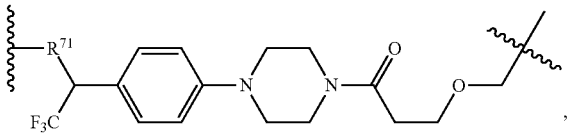

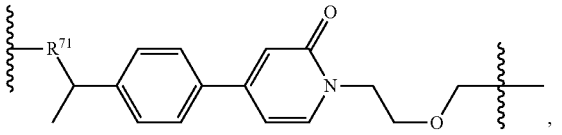

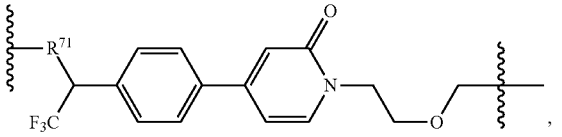

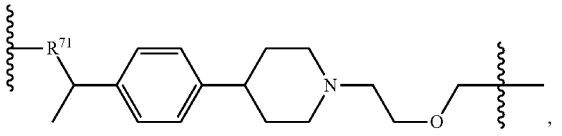

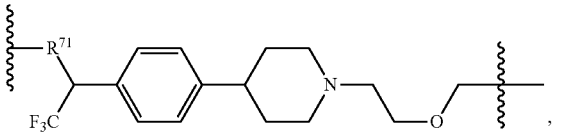

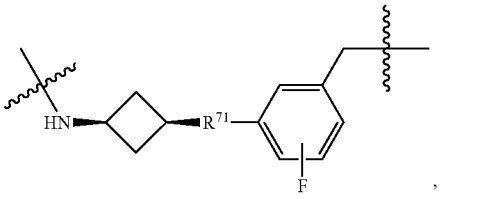

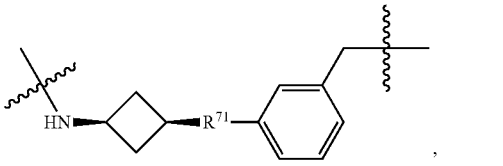

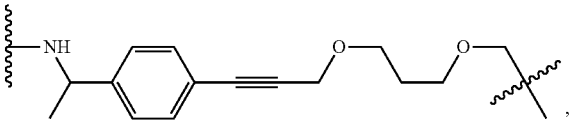

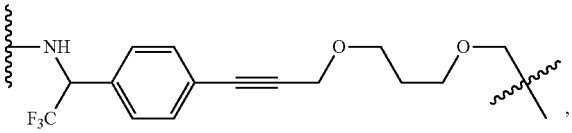

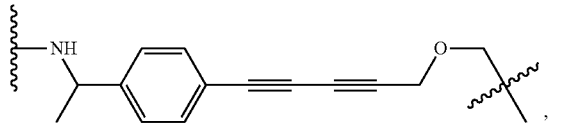

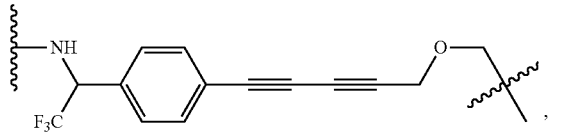

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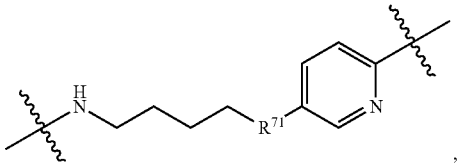

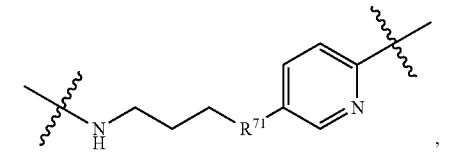

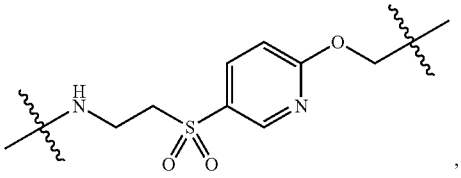

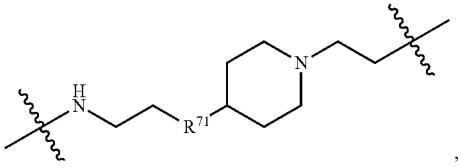

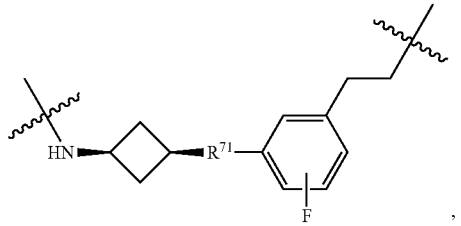

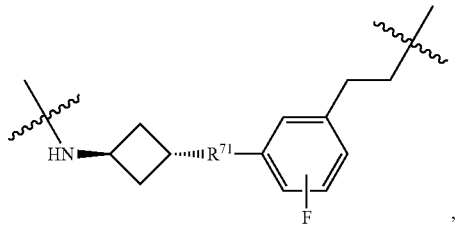

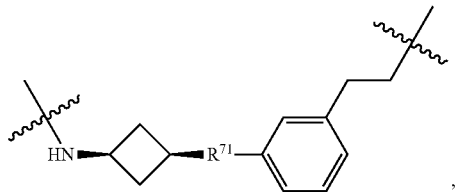

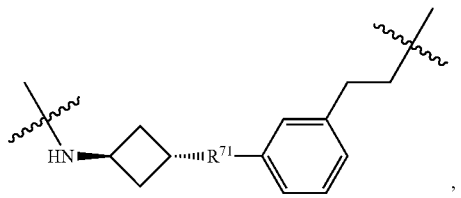

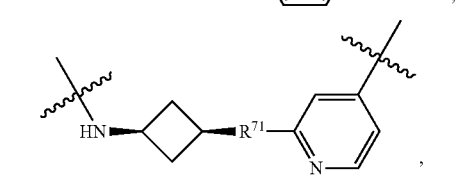

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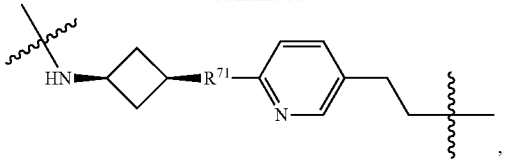

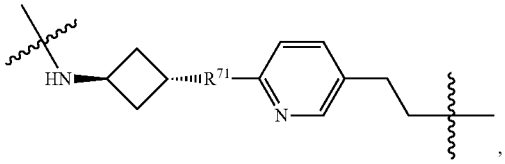

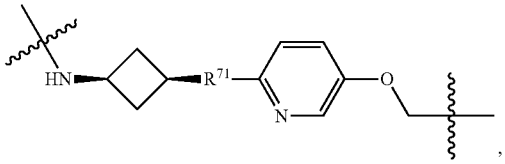

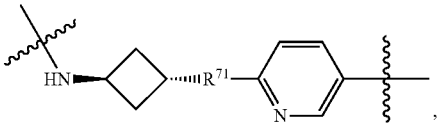

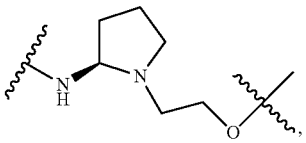

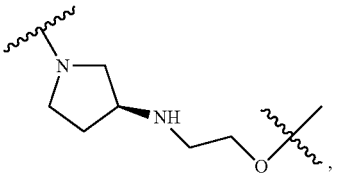

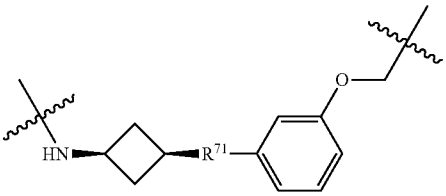

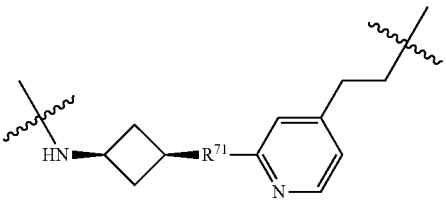

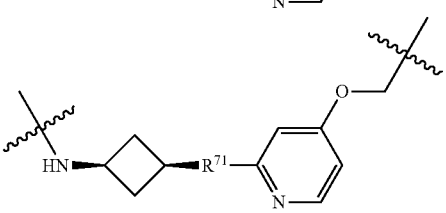

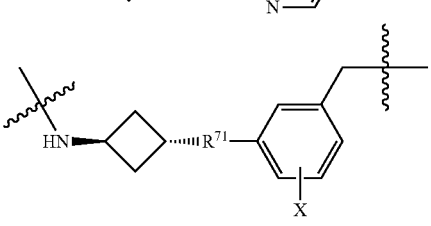

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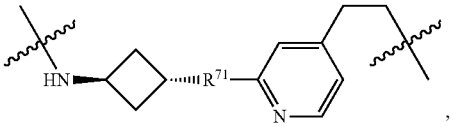

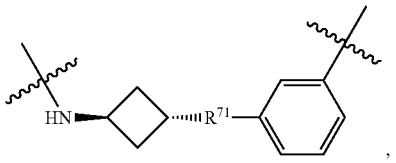

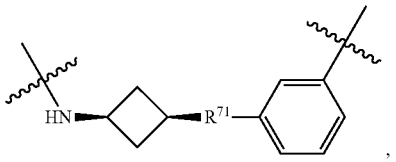

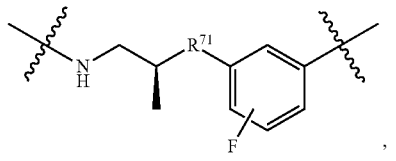

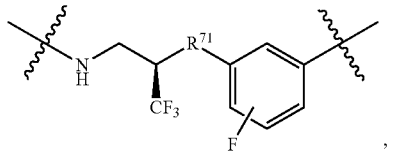

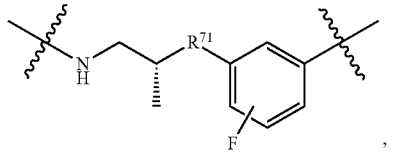

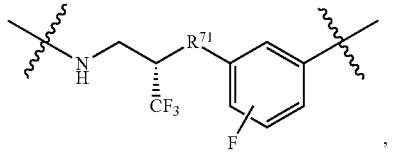

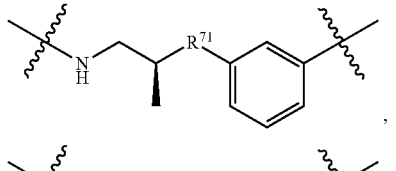

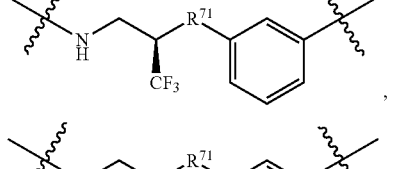

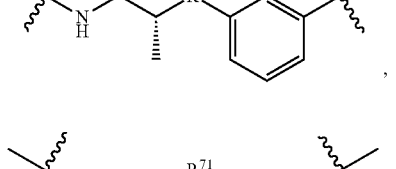

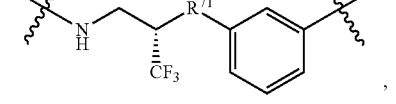

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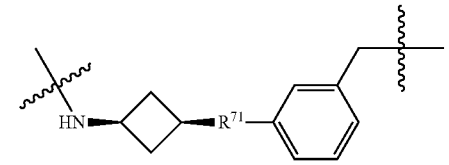

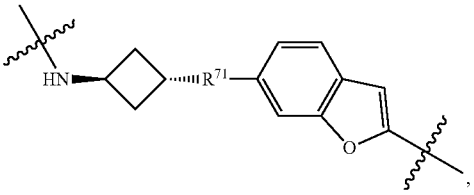

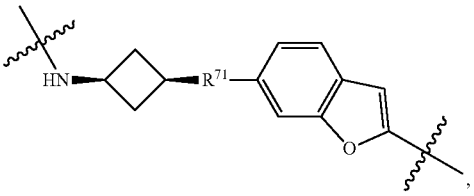

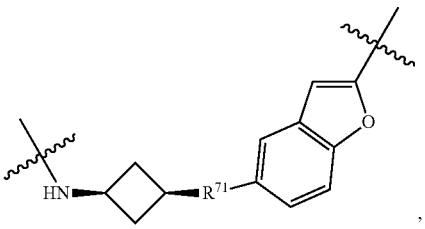

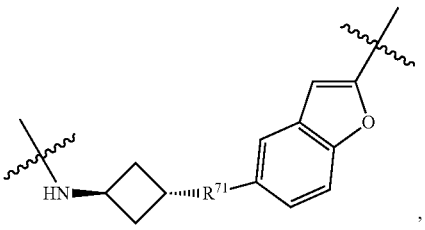

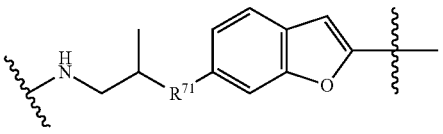

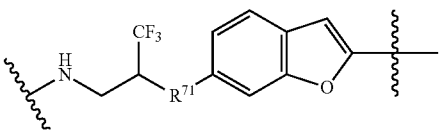

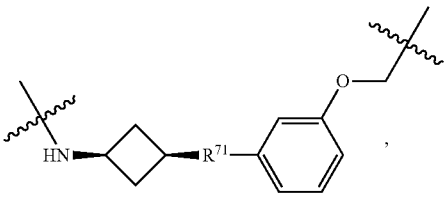

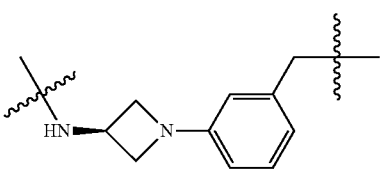

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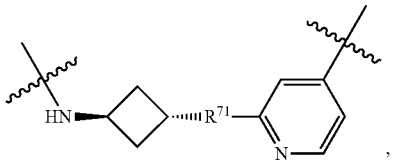

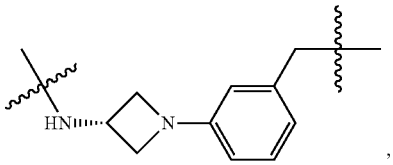

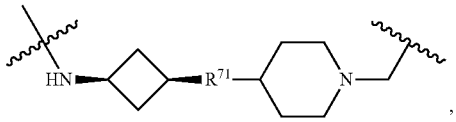

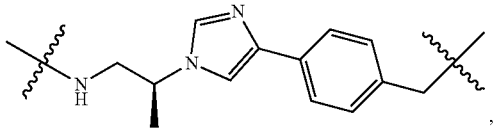

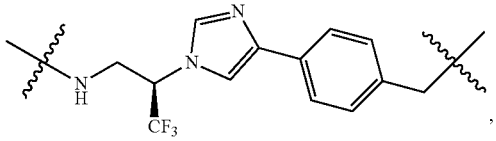

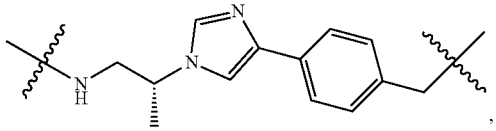

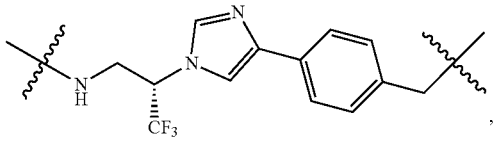

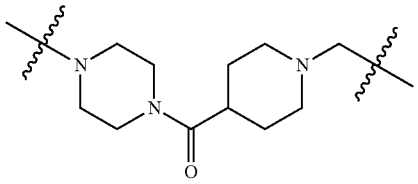

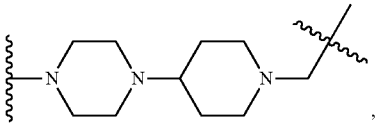

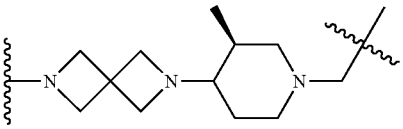

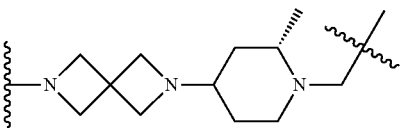

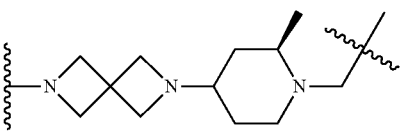

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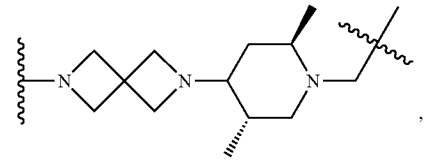

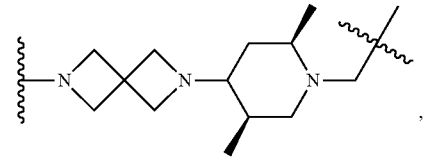

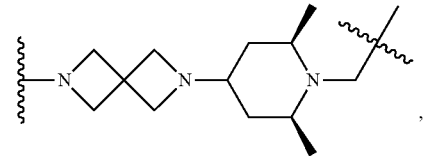

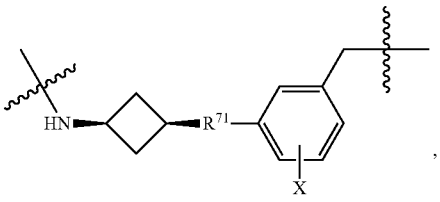

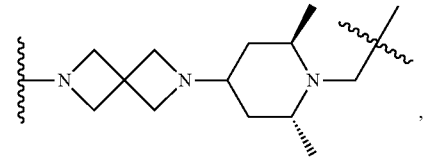

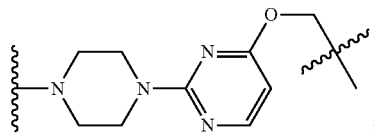

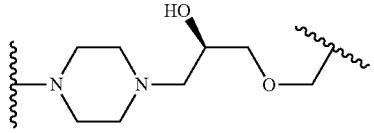

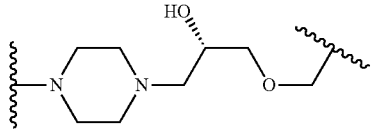

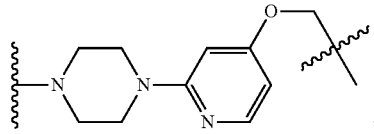

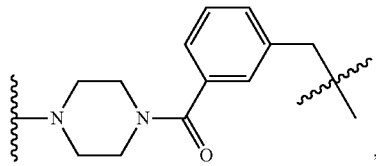

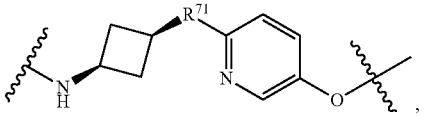

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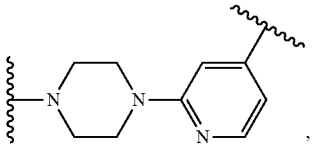

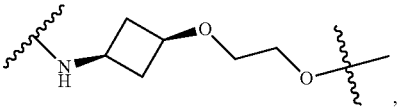

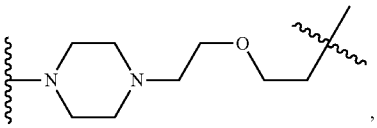

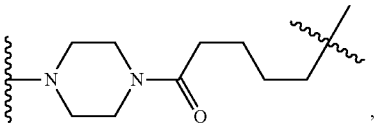

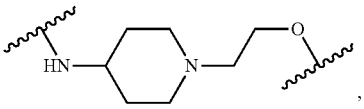

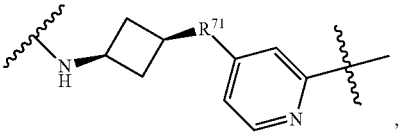

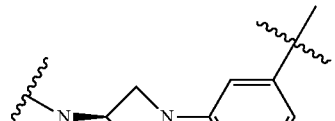

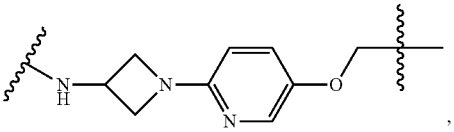

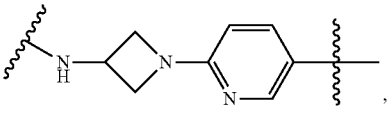

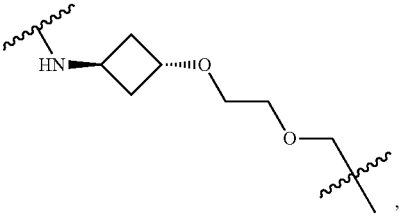

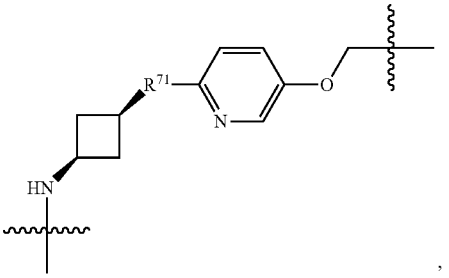

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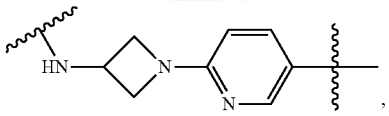
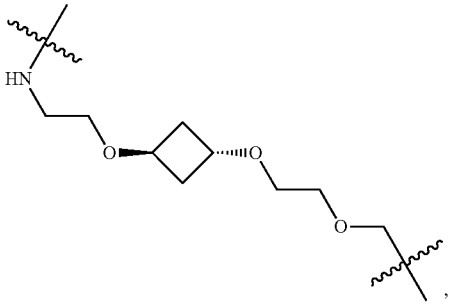
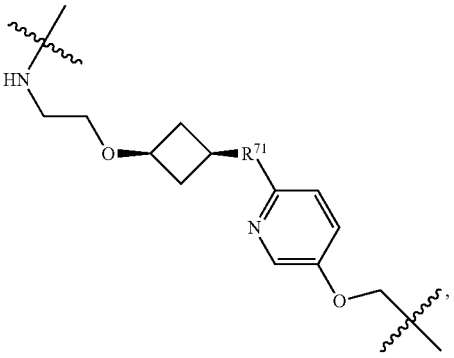
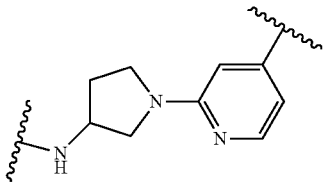
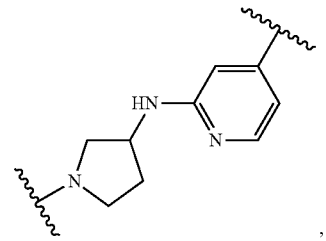
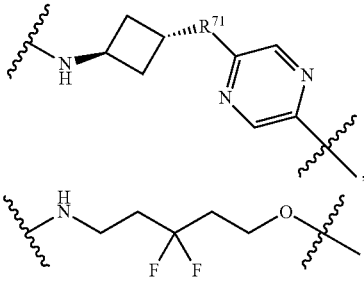






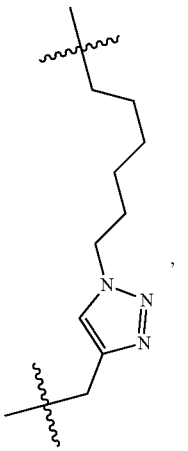


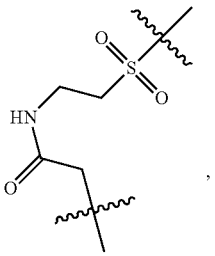


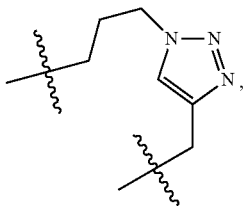


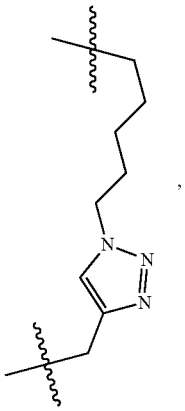
wherein R^{71} is —O—, —NH, —NMe, —Nalkyl, N(aliphatic), —N(heteroaliphatic).

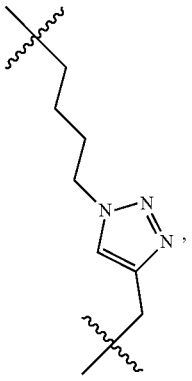
In additional embodiments, the Linker is selected from:

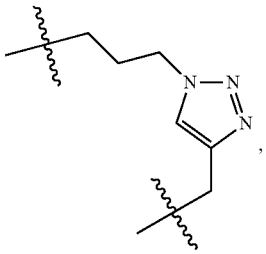


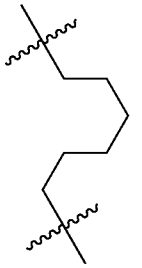












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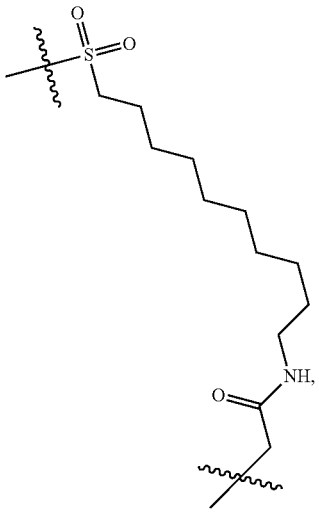

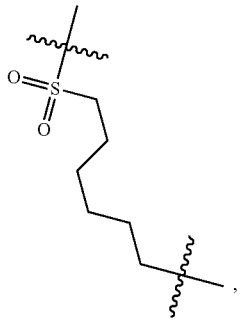

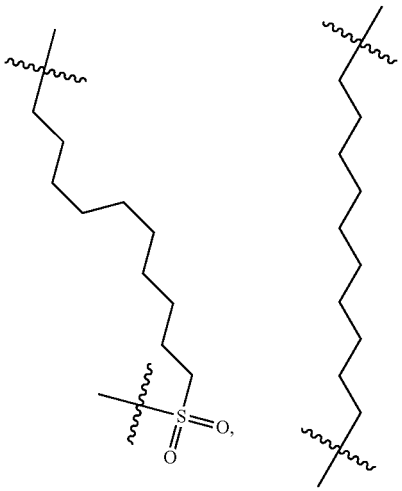

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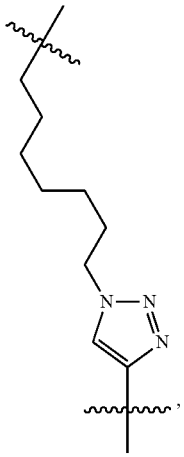

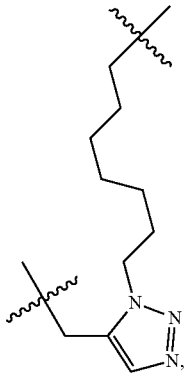

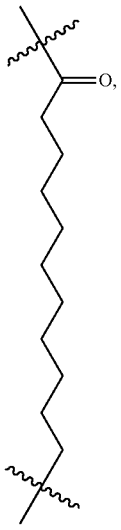

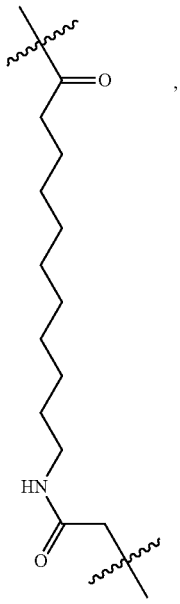

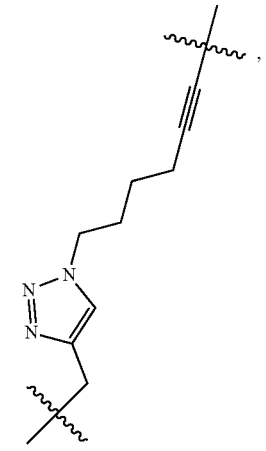

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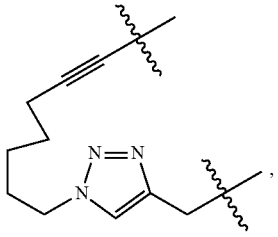

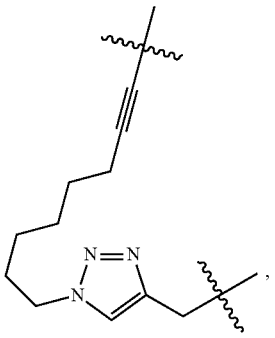

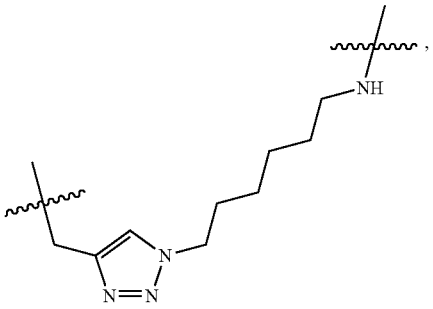

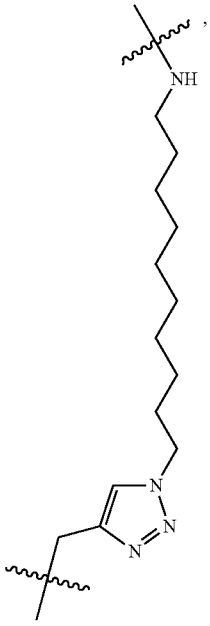

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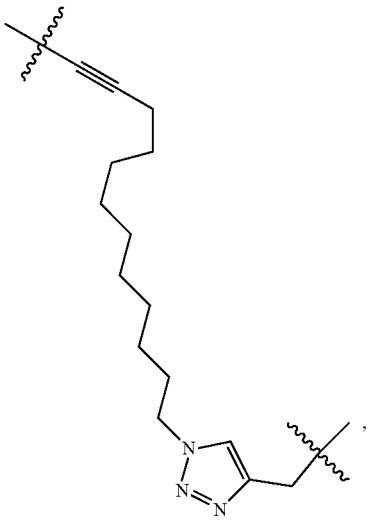

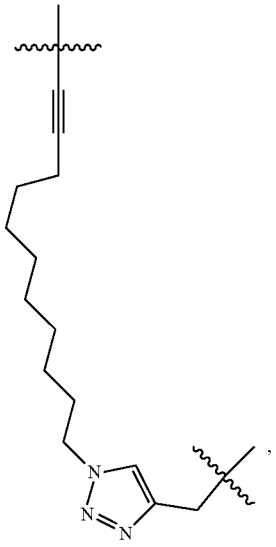

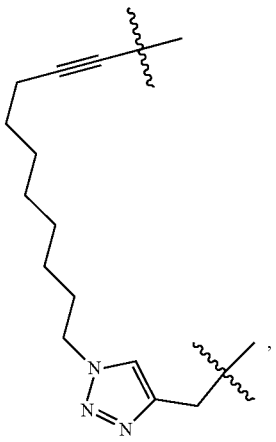

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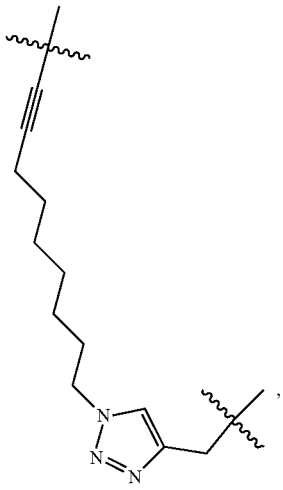

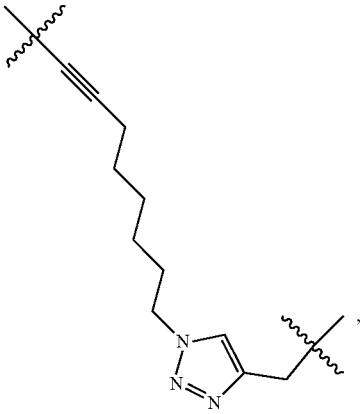

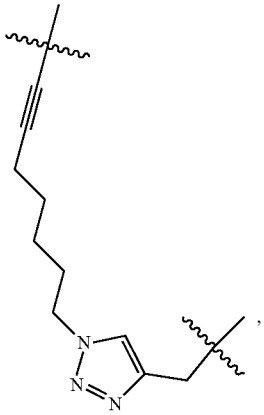

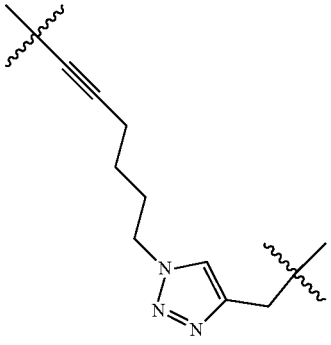

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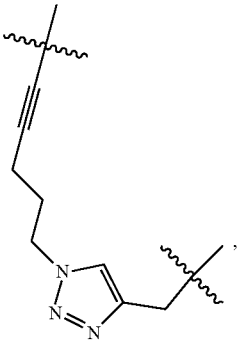

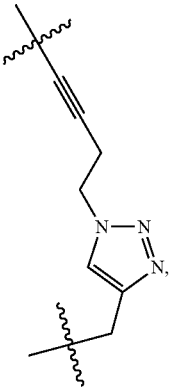

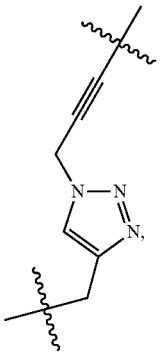

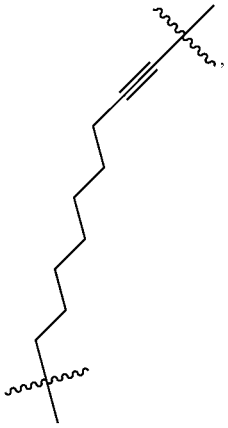

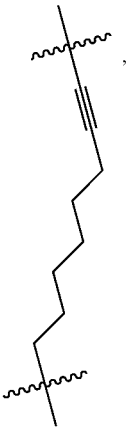

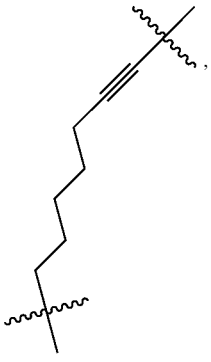

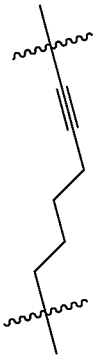

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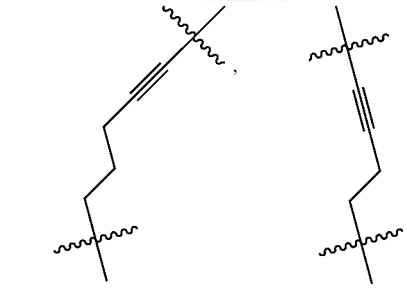

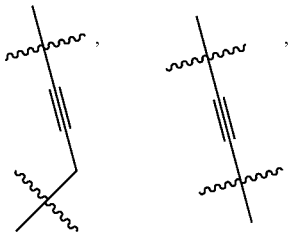

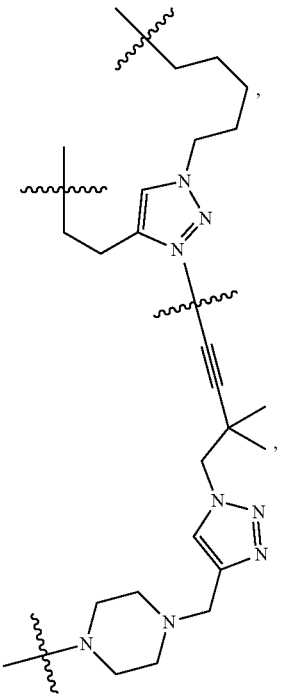

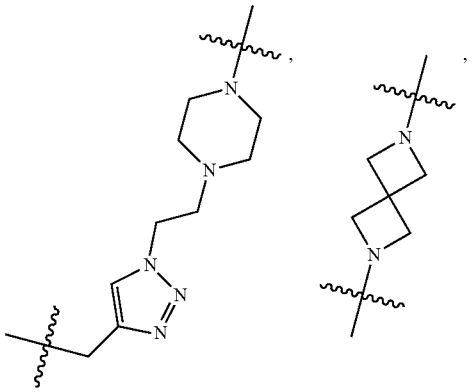

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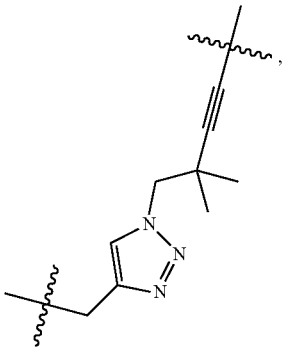

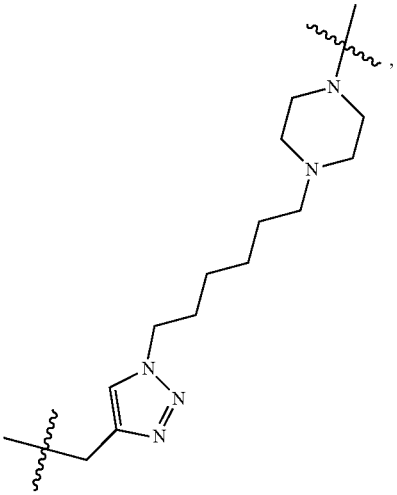

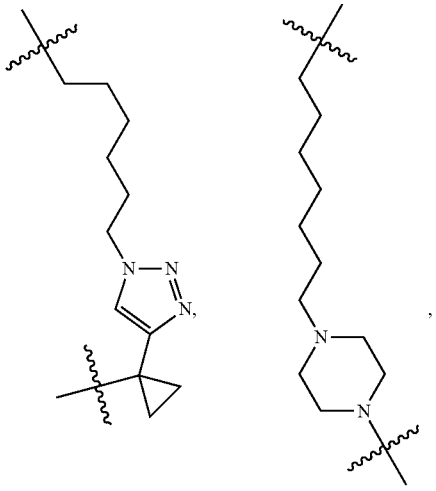

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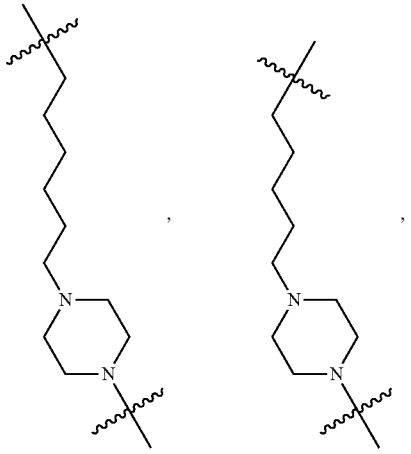

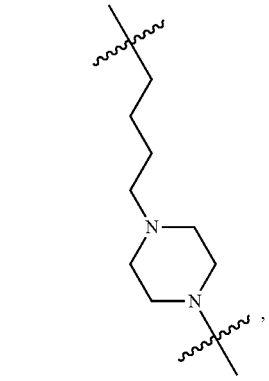

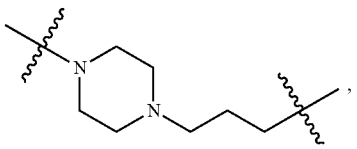

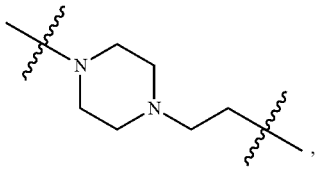

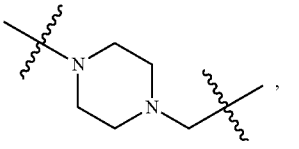

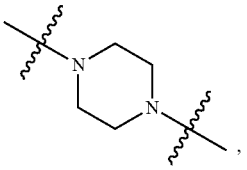

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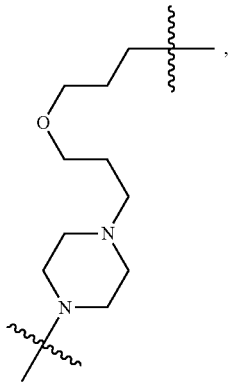

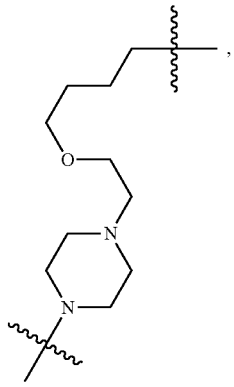

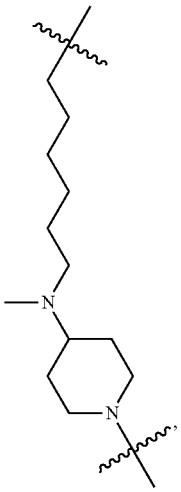

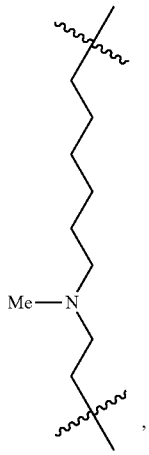

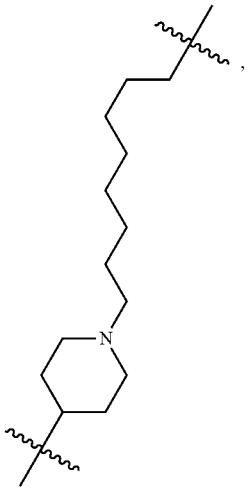

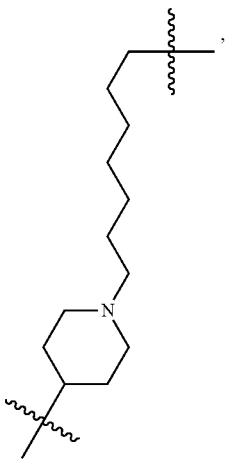

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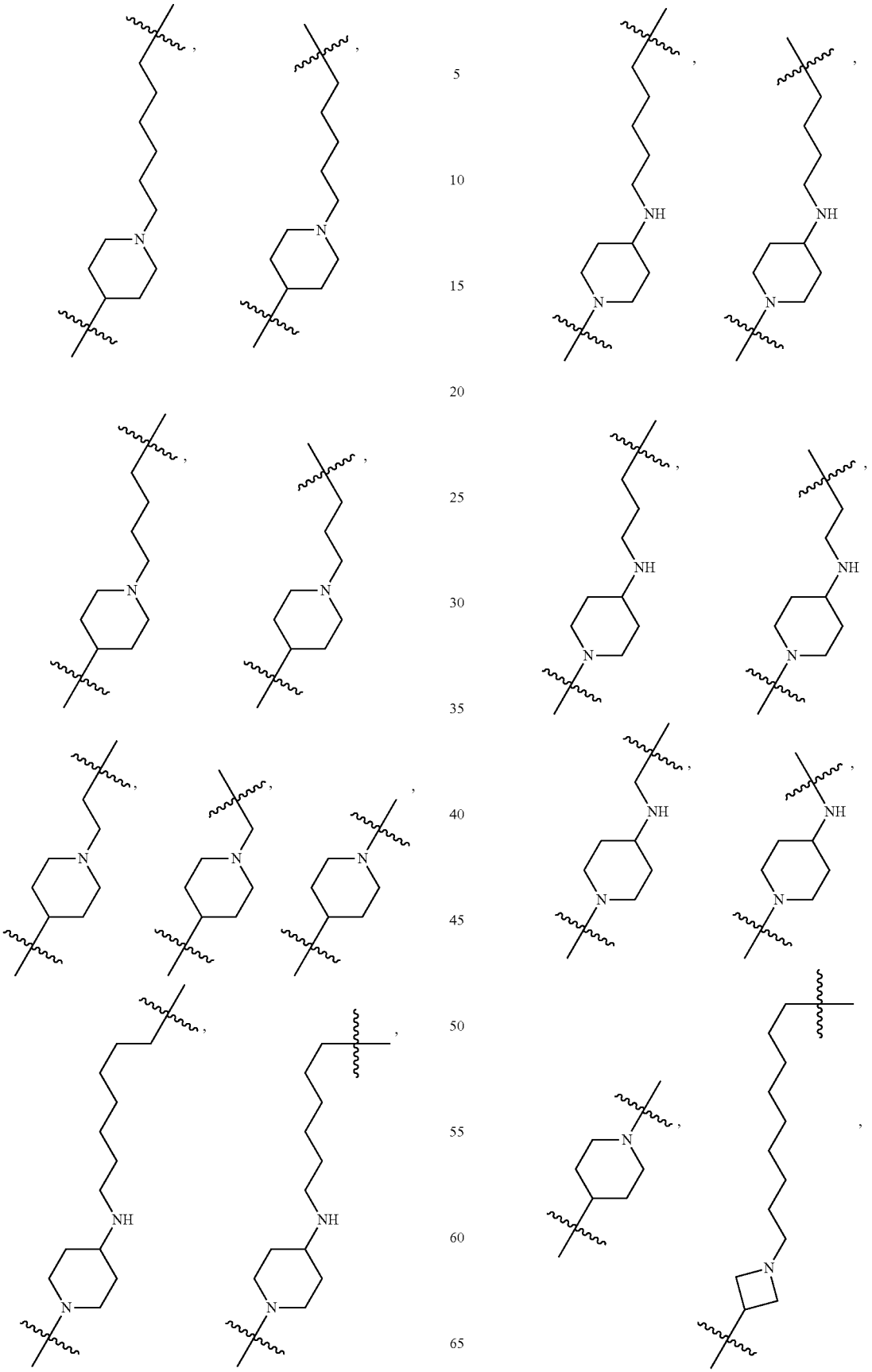

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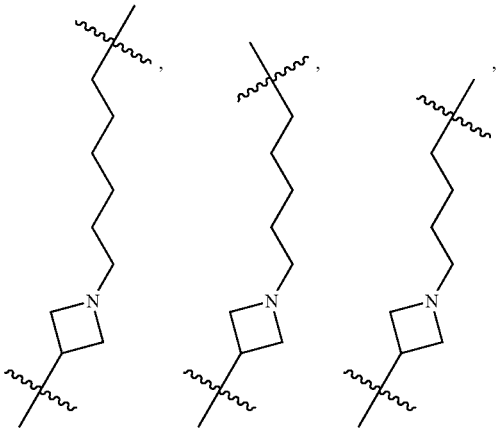

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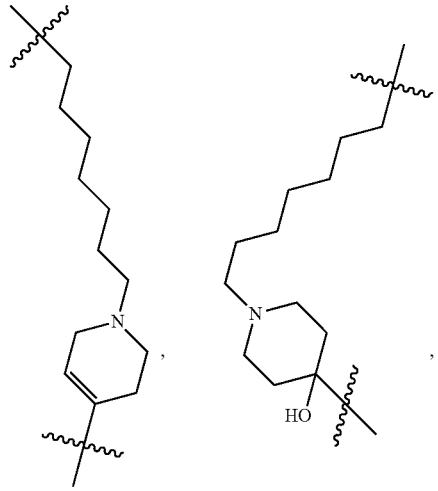

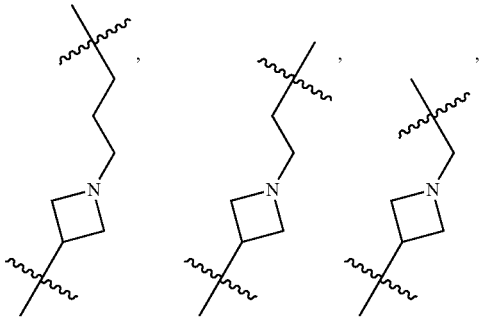

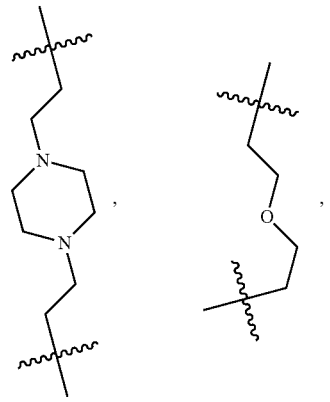

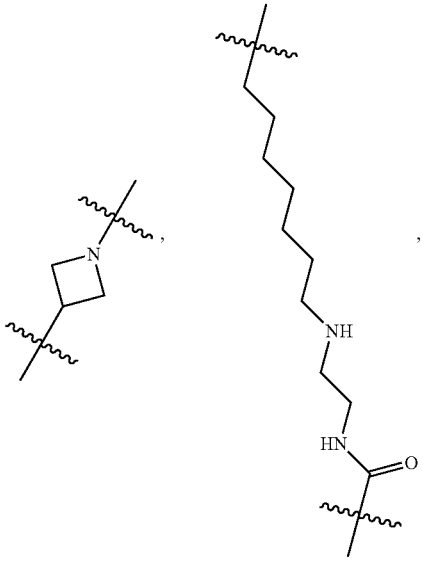

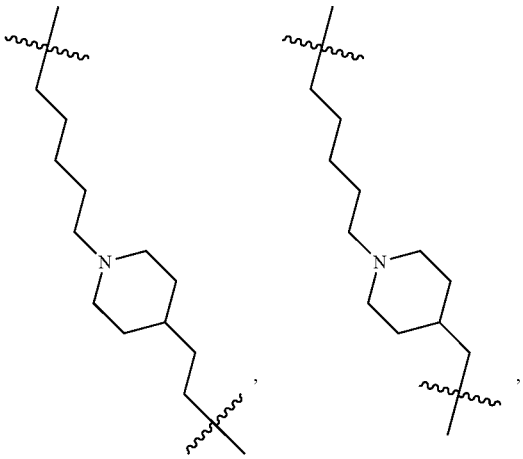

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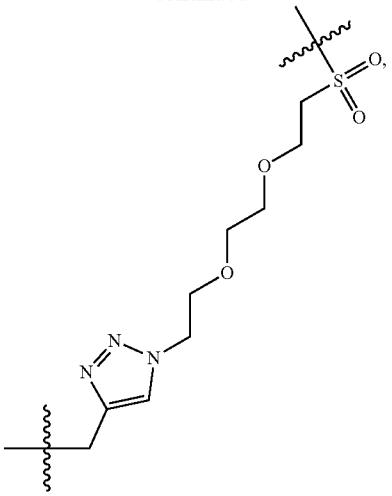

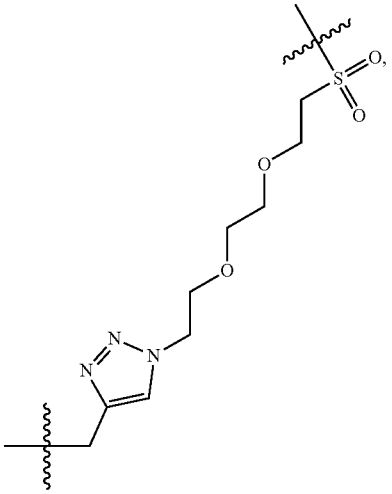

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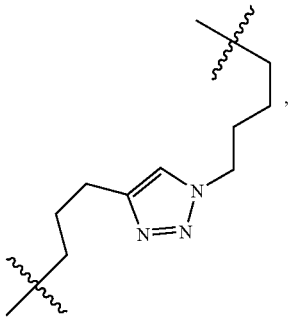

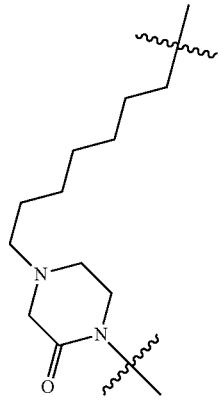

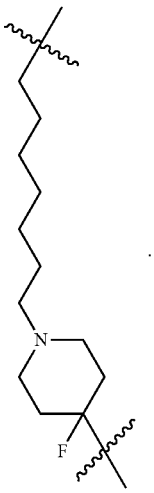

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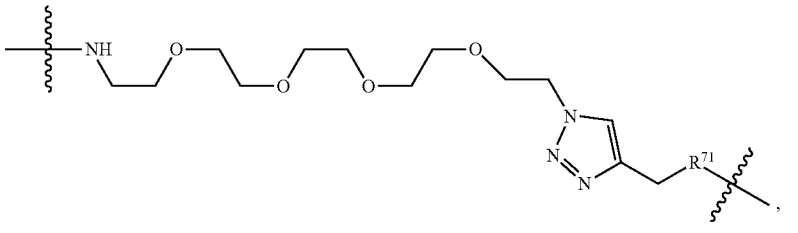

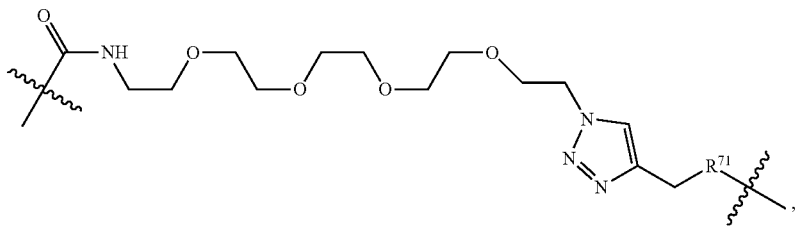

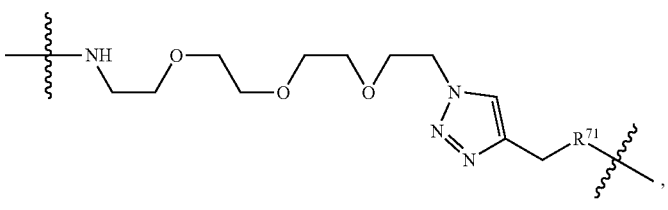

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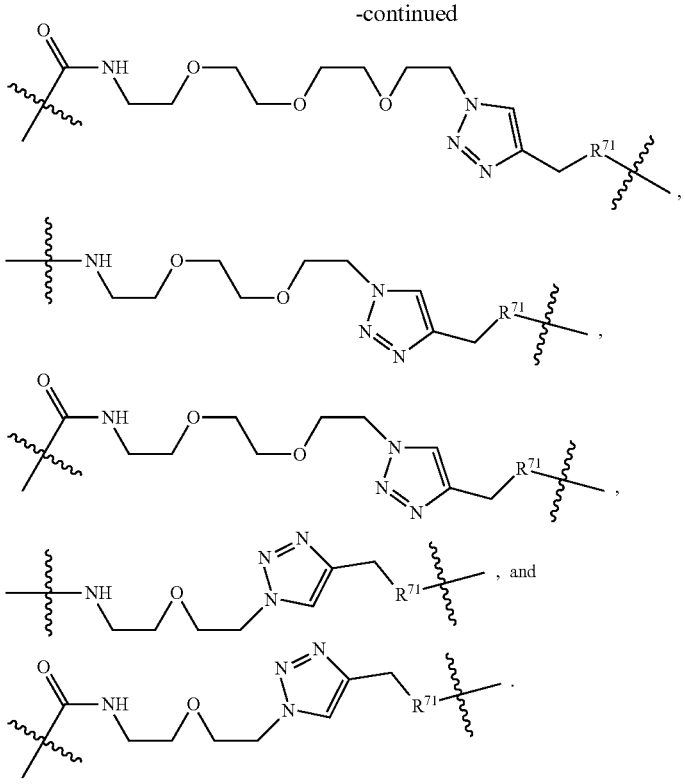

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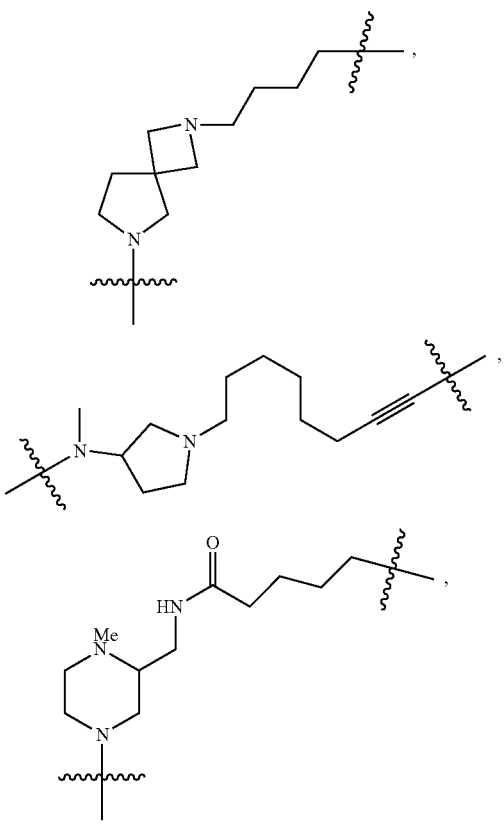

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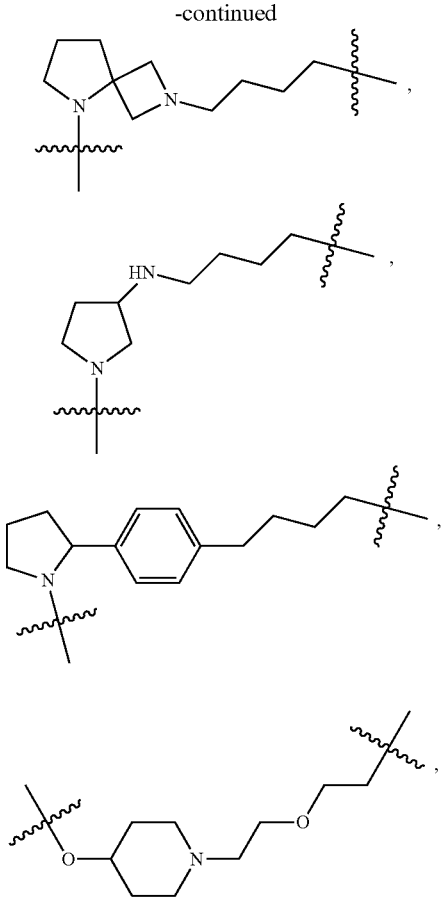

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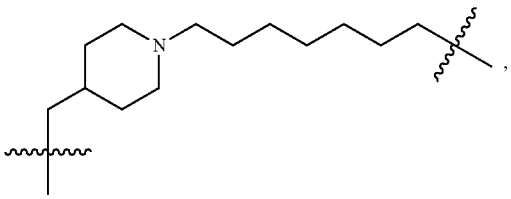

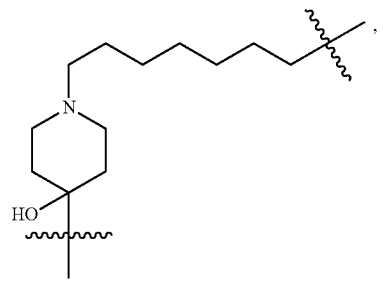

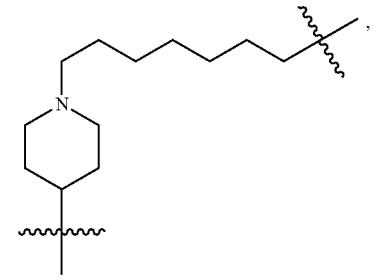

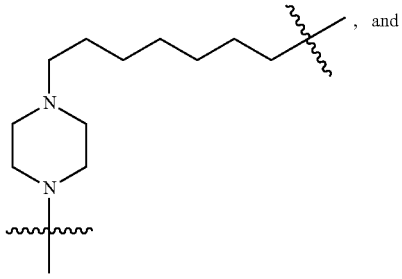

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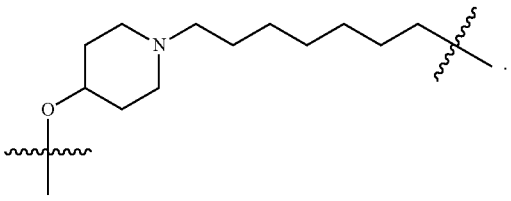

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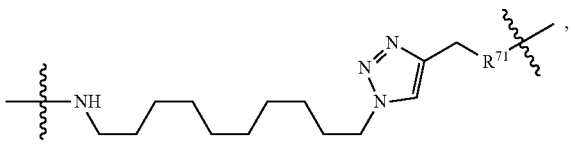

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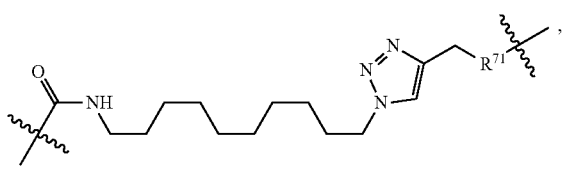

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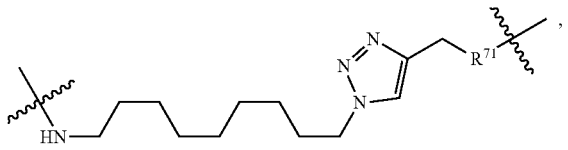

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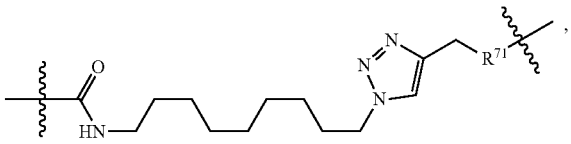

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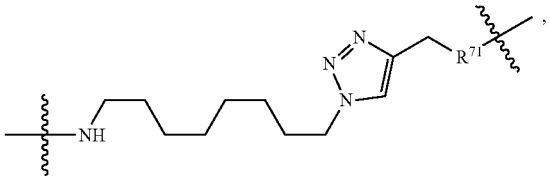

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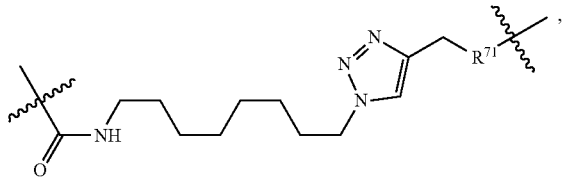

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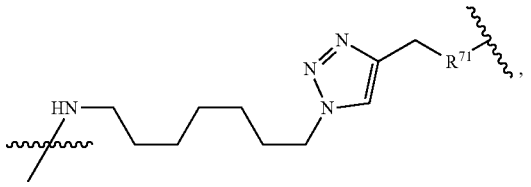

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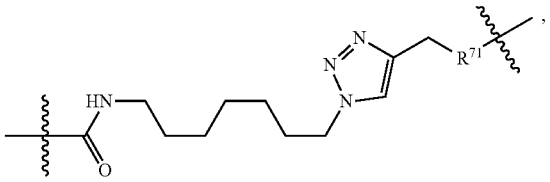

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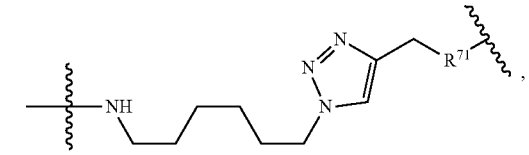

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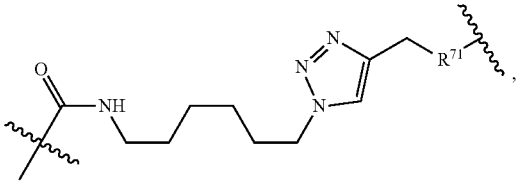

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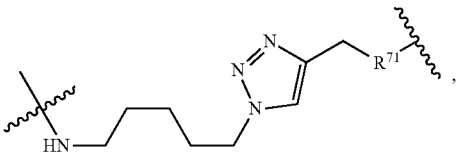

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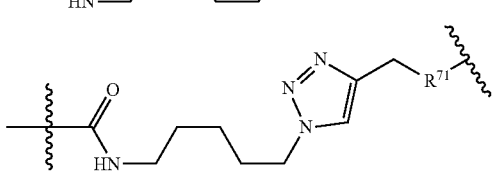

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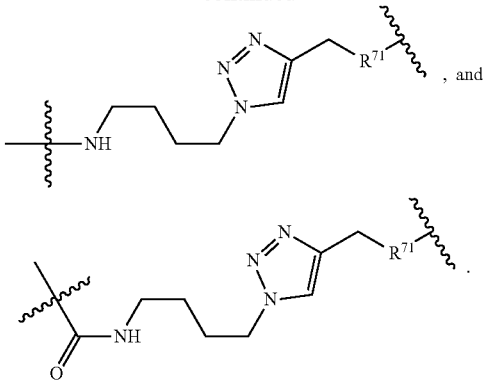
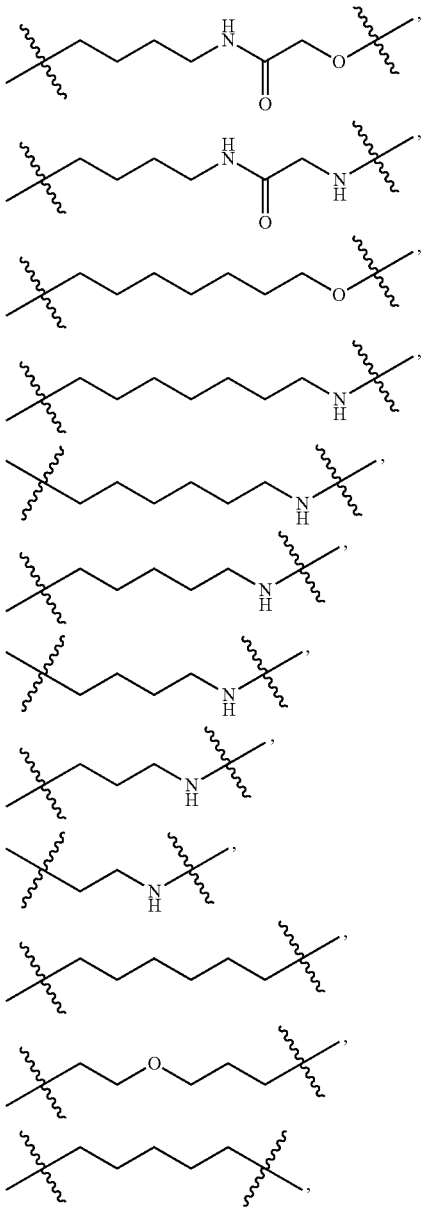


In additional embodiments, the Linker is selected from:



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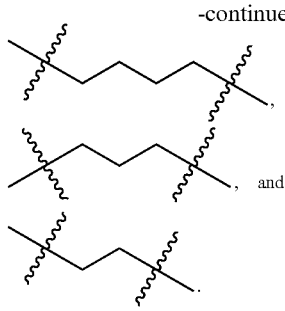
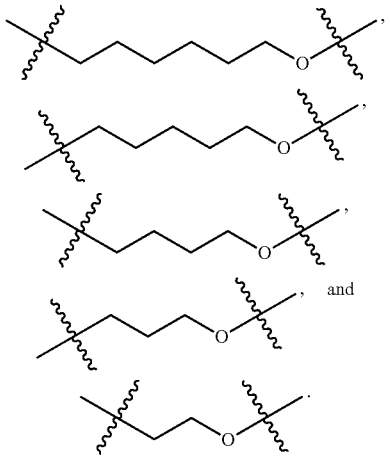


In additional embodiments, the Linker is selected from:



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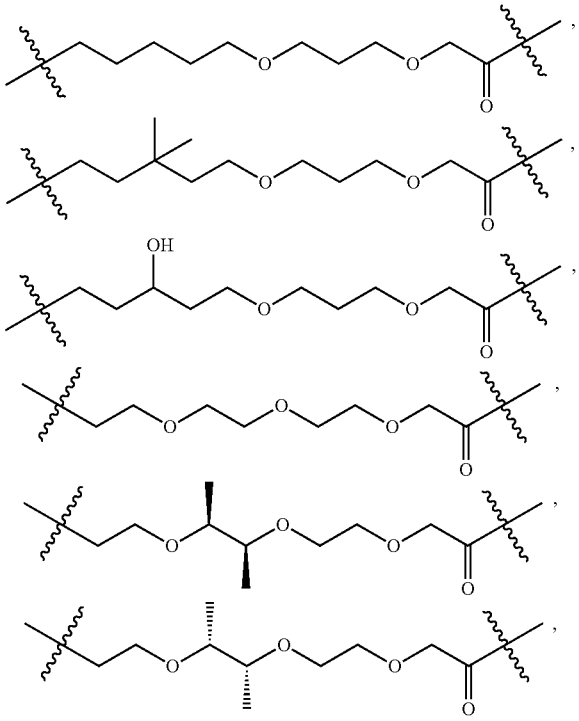

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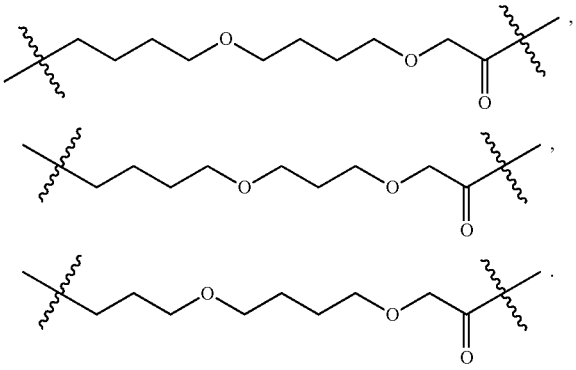
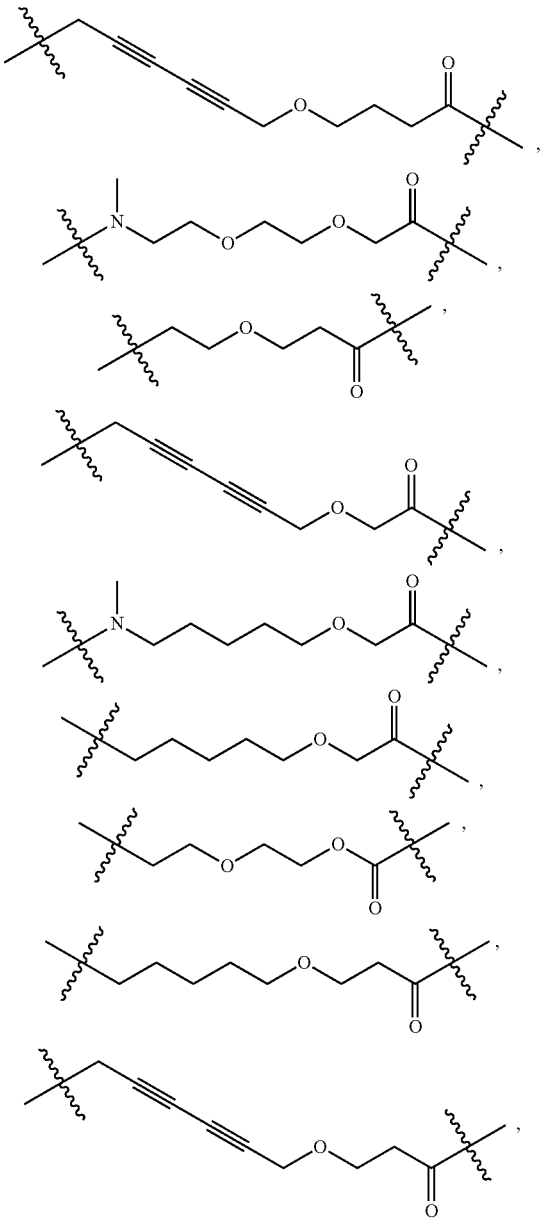


In certain embodiments the Linker is selected from:



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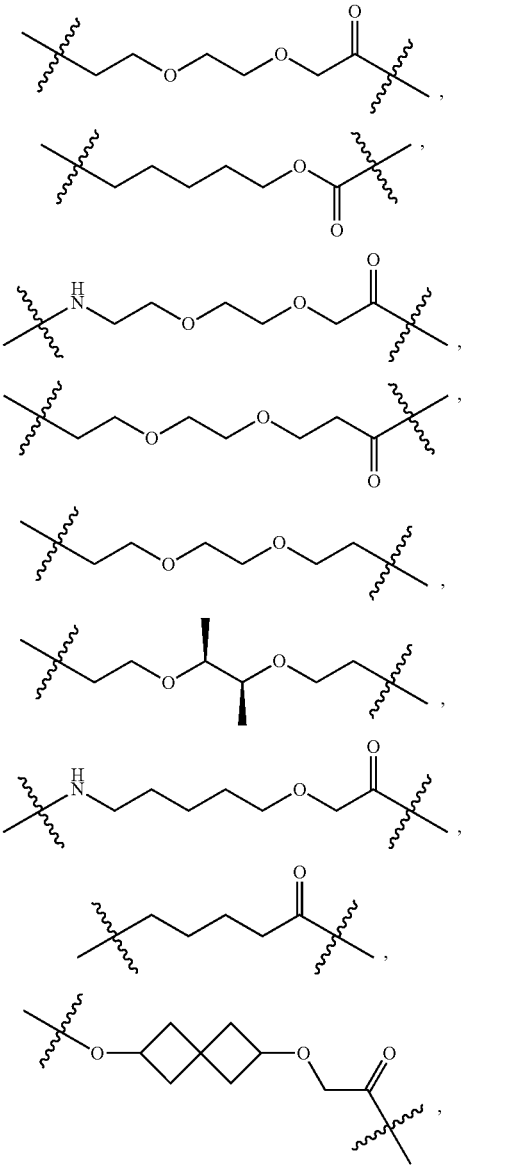

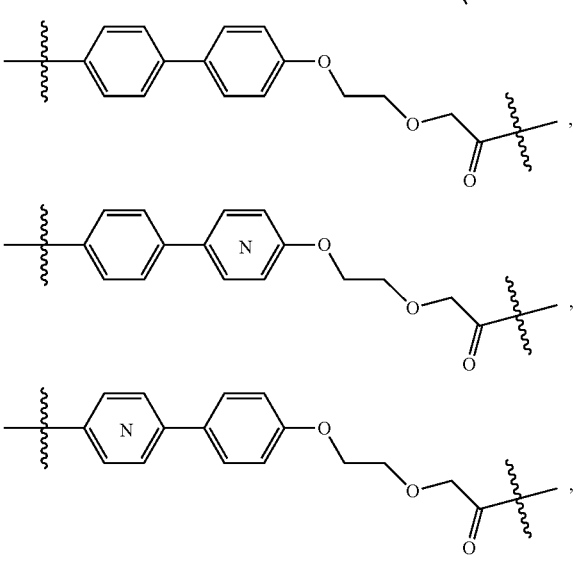

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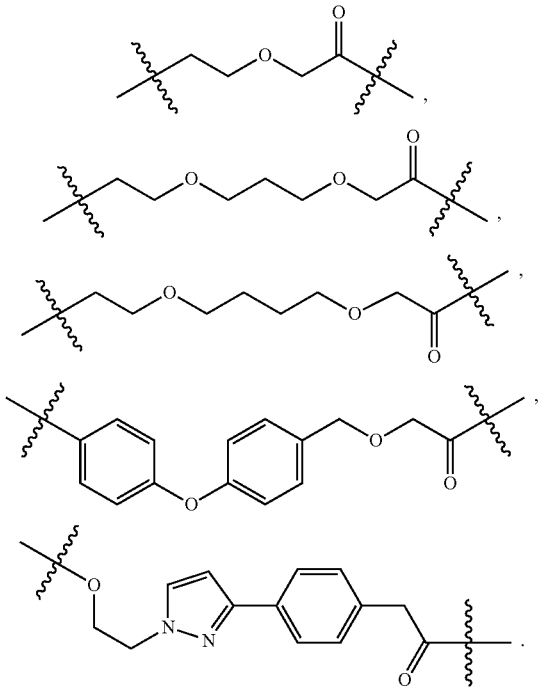
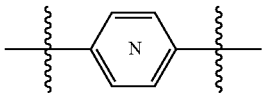
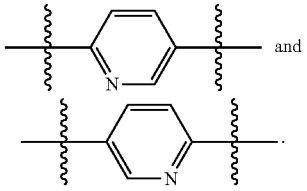


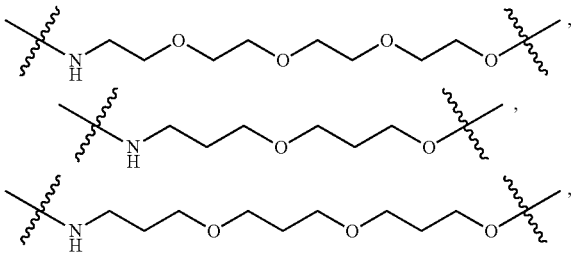
In the above structures



represents



In certain embodiments, Linker can be a 4-24 carbon atom linear chains, wherein one or more the carbon atoms in the linear chain can be replaced or substituted with oxygen, nitrogen, amide, fluorinated carbon, etc., such as the following:



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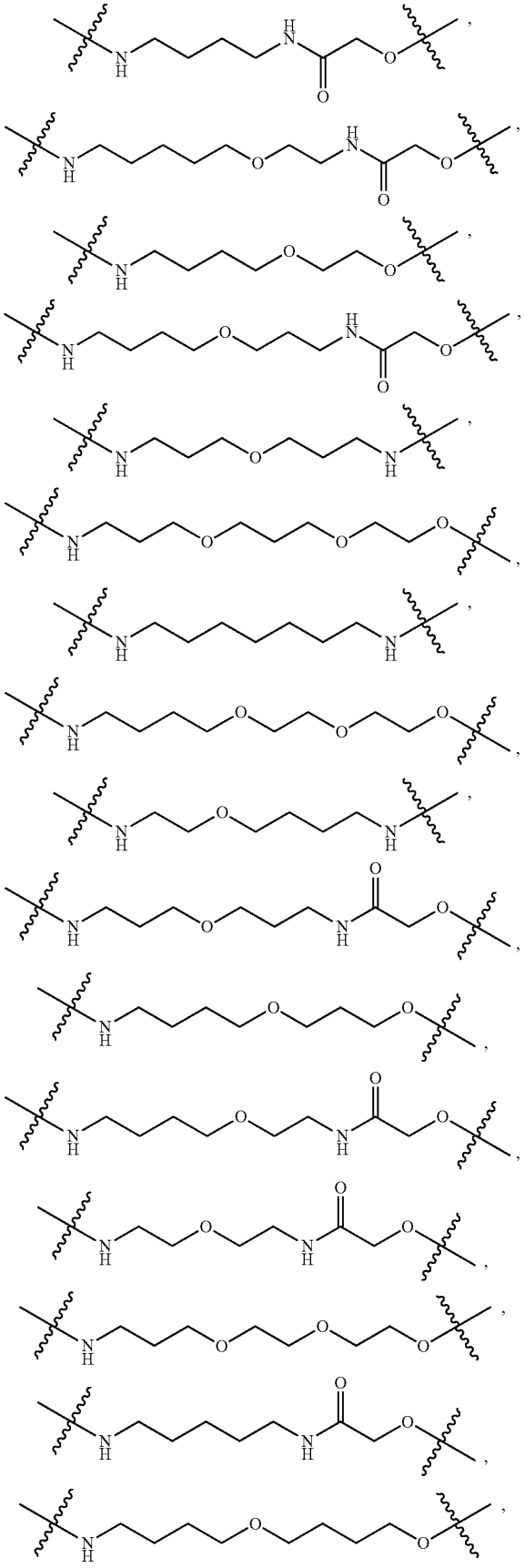

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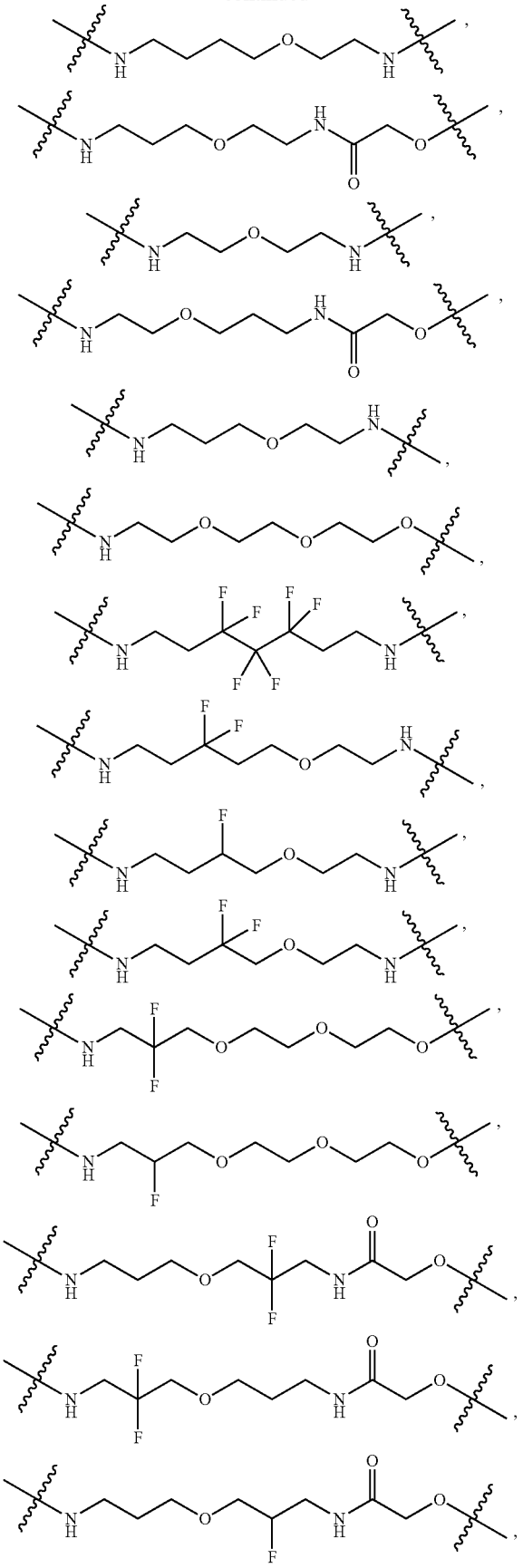

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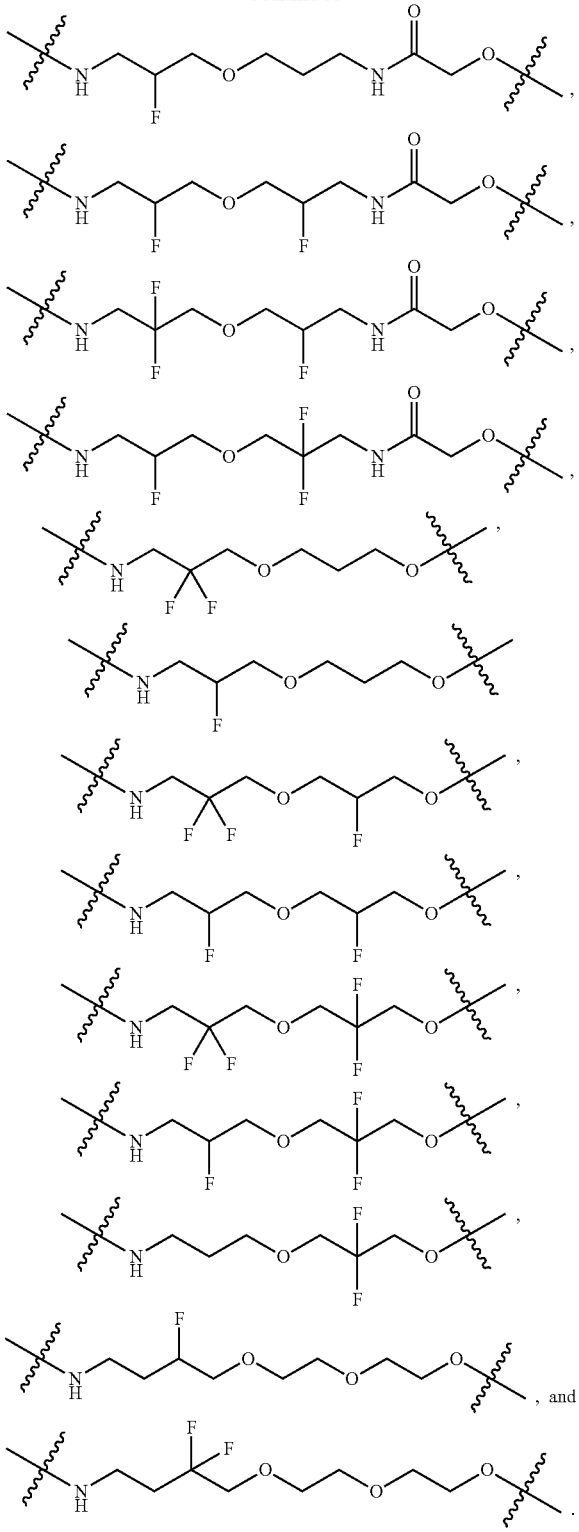
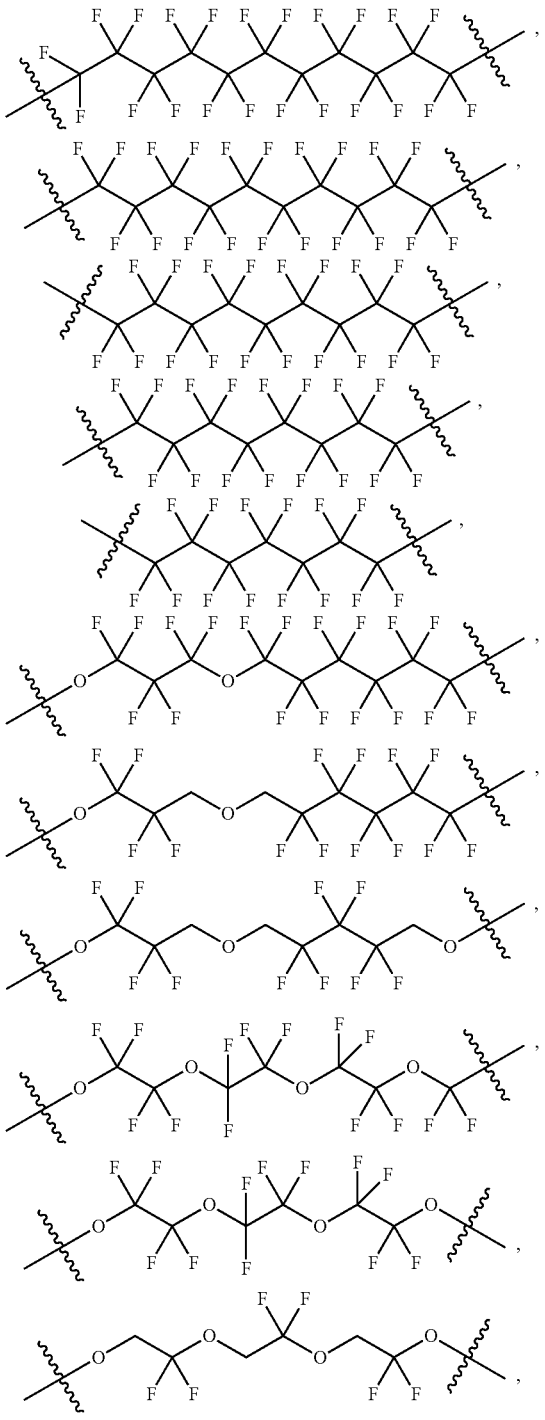


In certain embodiments, Linker can be a nonlinear chain, and can be, or include, aliphatic or aromatic or heteroaromatic cyclic moieties.

In certain embodiments, the Linker may include contiguous, partially contiguous or non-contiguous ethylene glycol unit groups ranging in size from about 1 to about 12 ethylene glycol units, between 1 and about 10 ethylene glycol units,

about 2 about 6 ethylene glycol units, between about 2 and 5 ethylene glycol units, between about 2 and 4 ethylene glycol units, for example, 1, 2, 3, 4, 6, 6, 7, 8, 9, 10, 11 or 12 ethylene glycol units.

In certain embodiments, the Linker may have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 fluorine substituents. In another embodiment the Linker is perfluorinated. In yet another embodiment the Linker is a partially or fully fluorinated poly ether. Nonlimiting examples of fluorinated Linkers include:



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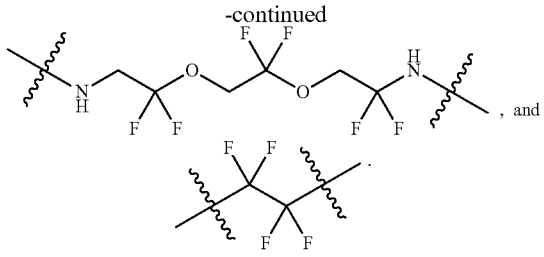

, and

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In certain embodiments, where the Target Ligand binds more than one protein (i.e., is not completely selective), selectivity may be enhanced by varying Linker length where the ligand binds some of its targets in different binding pockets, e.g., deeper or shallower binding pockets than others. Therefore, the length can be adjusted as desired.

Target Proteins

Degradation of cellular proteins is required for cell homeostasis and normal cell function, such as proliferation, differentiation and cell death. When this system becomes dysfunctional or does not identify and abate abnormal protein behavior in vivo, a disease state can arise in a host, such as a human. A large range of proteins can cause, modulate or amplify diseases in vivo, as well known to those skilled in the art, published in literature and patent filings as well as presented in scientific presentations.

Therefore, in one embodiment, a selected Degronimer compound of the present invention can be administered in vivo in an effective amount to a host in need thereof to degrade a selected protein that mediates a disorder to be treated. The selected protein target may modulate a disorder in a human via a mechanism of action such as modification of a biological pathway, pathogenic signaling or modulation of a signal cascade or cellular entry. In one embodiment, the Target Protein is a protein that is not drugable in the classic sense in that it does not have a binding pocket or an active site that can be inhibited or otherwise bound, and cannot be easily allosterically controlled. In another embodiment, the Target Protein is a protein that is drugable in the classic sense, yet for therapeutic purposes, degradation of the protein is preferred to inhibition.

The Target Protein is recruited with a Targeting Ligand for the Target Protein. Typically the Targeting Ligand binds the Target Protein in a non-covalent fashion. In an alternative embodiment, the Target Protein is covalently bound to the Degron in a manner that can be irreversible or reversible.

In one embodiment, the selected Target Protein is expressed from a gene that has undergone an amplification, translocation, deletion, or inversion event which causes or is caused by a medical disorder. In certain aspects, the selected Target Protein has been post-translationally modified by one, or a combination, of phosphorylation, acetylation, acylation including propionylation and crotylation, N-linked glycosylation, amidation, hydroxylation, methylation and polymethylation, O-linked glycosylation, pyrogultamoylation, myristoylation, farnesylation, geranylgeranylation, ubiquitination, sumoylation, or sulfation which causes or is caused by a medical disorder.

As contemplated herein, the present invention includes an Degronimer with a Targeting Ligand that binds to a Target Protein of interest. The Target Protein is any amino acid sequence to which an Degronimer can be bound which by degradation thereof, causes a beneficial therapeutic effect in

vivo. In one embodiment, the Target Protein is a non-endogenous peptide such as that from a pathogen or toxin. In another embodiment, the Target Protein can be an endogenous protein that mediates a disorder. The endogenous protein can be either the normal form of the protein or an aberrant form. For example, the Target Protein can be a mutant protein found in cancer cells, or a protein, for example, where a partial, or full, gain-of-function or loss-of-function is encoded by nucleotide polymorphisms. In some embodiments, the Degronimer targets the aberrant form of the protein and not the normal form of the protein. In another embodiment, the Target Protein can mediate an inflammatory disorder or an immune disorder, including an auto-immune disorder. In one embodiment, the Target Protein is a non-endogenous protein from a virus, as non-limiting examples, HIV, HBV, HCV, RSV, HPV, CMV, flavivirus, pestivirus, coronavirus, noroviridae, etc. In one embodiment, the Target Protein is a non-endogenous protein from a bacteria, which may be for example, a gram positive bacteria, gram negative bacteria or other, and can be a drug-resistant form of bacteria. In one embodiment, the Target Protein is a non-endogenous protein from a fungus. In one embodiment, the Target Protein is a non-endogenous protein from a prion. In one embodiment, the Target Protein is a protein derived from a eukaryotic pathogen, for example a protist, helminth, etc.

In one aspect, the Target Protein mediates chromatin structure and function. The Target Protein may mediate an epigenetic action such as DNA methylation or covalent modification of histones. An example is histone deacetylase (HDAC 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11). Alternatively, the Target Protein may be a bromodomain, which are readers of lysine acetylation (for example, BRD1, 2, 3, 4, 5, 6, 7, 8, 9 and T. FIG. **9** illustrates the proteins of the bromodomain family, which, for example, can act as Target Proteins according to the present invention.

Other nonlimiting examples of Target Proteins are a structural protein, receptor, enzyme, cell surface protein, a protein involved in apoptotic signaling, aromatase, helicase, mediator of a metabolic process (anabolism or catabolism), antioxidant, protease, kinase, oxidoreductase, transferase, hydrolase, lyase, isomerase, ligase, enzyme regulator, signal transducer, structural molecule, binding activity (protein, lipid carbohydrate), cell motility protein, membrane fusion protein, cell communication mediator, regulator of biological processes, behavioral protein, cell adhesion protein, protein involved in cell death, protein involved in transport (including protein transporter activity, nuclear transport, ion transporter, channel transporter, carrier activity, permease, secretase or secretion mediator, electron transporter, chaperone regulator, nucleic acid binding, transcription regulator, extracellular organization and biogenesis regulator, and translation regulator).

In one embodiment, the Target Protein is a modulator of a signaling cascade related to a known disease state. In another embodiment, the Target Protein mediates a disorder by a mechanism different from modulating a signaling cascade. Any protein in a eukaryotic system or a microbial system, including a virus, bacteria or fungus, as otherwise described herein, are targets for proteasomal degradation using the present invention. The Target Protein may be a eukaryotic protein, and in some embodiments, a human protein.

In one embodiment, the Target Protein is RXR, DHFR, Hsp90, a kinase, HDM2, MDM2, BET bromodomain-containing protein, HDAC, IDH1, Mcl-1, human lysine methyltransferase, a nuclear hormone receptor, aryl hydrocarbon receptor (AHR), RAS, RAF, FLT, SMARC, KSR, NF2L, CTNB, CBLB, BCL.

In one embodiment, a bromodomain containing protein has histone acetyl transferase activity.

In one embodiment, the bromodomain containing protein is BRD2, BRD3, BRD4, BRDT or ASH1L.

In one embodiment, the bromodomain containing protein is a non-BET protein.

In one embodiment, the non-BET protein is BRD7 or BRD9.

In one embodiment, the FLT is not FLT 3. In one embodiment, the RAS is not RASK. In one embodiment, the RAF is not RAF1. In one embodiment, the SMARC is not SMARC2. In one embodiment, the KSR is not KSR1. In one embodiment, the NF2L is not NF2L2. In one embodiment, the CTNB is not CTNB 1. In one embodiment, the BCL is not BCL6.

In one embodiment, the Target Protein is selected from: EGFR, FLT3, RAF 1, SMRCA2, KSR1, NF2L2, CTNB1, CBLB, BCL6, and RASK.

In another embodiment, the Target Protein is not selected from: EGFR, FLT3, RAF1, SMRCA2, KSR1, NF2L2, CTNB1, CBLB, BCL6, and RASK.

In one embodiment, the Targeting Ligand is an EGFR ligand, a FLT3 ligand, a RAF 1 ligand, a SMRCA2 ligand, a KSR1 ligand, a NF2L2 ligand, a CTNB 1 ligand, a CBLB ligand, a BCL6 ligand, or a RASK ligand.

In one embodiment, the Targeting Ligand is not a EGFR ligand, a FLT3 ligand, a RAF 1 ligand, a SMRCA2 ligand, a KSR1 ligand, a NF2L2 ligand, a CTNB 1 ligand, a CBLB ligand, a BCL6 ligand, or a RASK ligand.

The present invention may be used to treat a wide range of disease states and/or conditions, including any disease state and/or condition in which a protein is dysregulated and where a patient would benefit from the degradation of proteins.

For example, a Target Protein can be selected that is a known target for a human therapeutic, and the therapeutic can be used as the Targeting Ligand when incorporated into the Degronimer according to the present invention. These include proteins which may be used to restore function in a polygenic disease, including for example B7.1 and B7, TINFR1m, TNFR2, NADPH oxidase, Bcl2/Bax and other partners in the apoptosis pathway, C_5a receptor, HMG-CoA reductase, PDE V phosphodiesterase type, PDE IV phosphodiesterase type 4, PDE I, PDEII, PDEIII, squalene cyclase inhibitor, CXCR1, CXCR2, nitric oxide (NO) synthase, cyclo-oxygenase 1, cyclo-oxygenase 2, 5HT receptors, dopamine receptors, G Proteins, e.g., Gq, histamine receptors, 5-lipoxygenase, tryptase serine protease, thymidylate synthase, purine nucleoside phosphorylase, GAPDH trypanosomal, glycogen phosphorylase, Carbonic anhydrase, chemokine receptors, JAW STAT, RXR and similar, HIV 1 protease, HIV 1 integrase, influenza, neuraminidase, hepatitis B reverse transcriptase, sodium channel, multi drug resistance (MDR), protein P-glycoprotein (and MRP), tyrosine kinases, CD23, CD124, tyrosine kinase p56 lck, CD4, CD5, IL-2 receptor, IL-1 receptor, TNF-alphaR, ICAM1, Cat+ channels, VCAM, VLA-4 integrin, selectins, CD40/CD40L, neurokinins and receptors, inosine monophosphate dehydrogenase, p38 MAP Kinase, Ras/Raf/MER/ERK pathway, interleukin-1 converting enzyme, caspase, HCV, NS3 protease, HCV NS3 RNA helicase, glycinamide ribonucleotide formyl transferase, rhinovirus 3C protease, herpes simplex virus-1 (HSV-I), protease, cytomegalovirus (CMV) protease, poly (ADP-ribose)

polymerase, cyclin dependent kinases, vascular endothelial growth factor, oxytocin receptor, microsomal transfer protein inhibitor, bile acid transport inhibitor, 5 alpha reductase inhibitors, angiotensin 11, glycine receptor, noradrenaline reuptake receptor, endothelin receptors, neuropeptide Y and receptor, estrogen receptors, androgen receptors, adenosine receptors, adenosine kinase and AMP deaminase, purinergic receptors (P2Y1, P2Y2, P2Y4, P2Y6, P2X1-7), farnesyltransferases, geranylgeranyl transferase, TrkA a receptor for NGF, beta-amyloid, tyrosine kinase Flk-IIKDR, vitronectin receptor, integrin receptor, Her-2/neu, telomerase inhibition, cytosolic phospholipaseA2 and EGF receptor tyrosine kinase. Additional protein targets include, for example, ecdysone 20-monooxygenase, ion channel of the GABA gated chloride channel, acetylcholinesterase, voltage-sensitive sodium channel protein, calcium release channel, and chloride channels. Still further Target Proteins include Acetyl-CoA carboxylase, adenylosuccinate synthetase, protoporphyrinogen oxidase, and enolpyruvylshikimate-phosphate synthase.

In certain embodiments, the Target Protein is derived from a kinase to which the Targeting Ligand is capable of binding or binds including, but not limited to, a tyrosine kinase (e.g., AATK, ABL, ABL2, ALK, AXL, BLK, BMX, BTK, CSF1R, CSK, DDR1, DDR2, EGFR, EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHA10, EPHB1, EPHB2, EPHB3, EPHB4, EPHB6, ERBB2, ERBB3, ERBB4, FER, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT3, FLT4, FRK, FYN, GSG2, HCK, IGF1R, ILK, INSR, INSRR, IRAK4, ITK, JAK1, JAK2, JAK3, KDR, KIT, KSR1, LCK, LMTK2, LMTK3, LTK, LYN, MATK, MERTK, MET, MLTK, MST1R, MUSK, NPR1, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PLK4, PTK2, PTK2B, PTK6, PTK7, RET, ROR1, ROR2, ROS1, RYK, SGK493, SRC, SRMS, STYK1, SYK, TEC, TEK, TEX14, TIE1, TNK1, TNK2, TNNI3K, TXK, TYK2, TYRO3, YES1, or ZAP70).

In certain embodiments, the Target Protein is derived from a kinase to which the Targeting Ligand is capable of binding or binds including, but not limited to, a serine/threonine kinase (e.g., casein kinase 2, protein kinase A, protein kinase B, protein kinase C, Raf kinases, CaM kinases, AKT1, AKT2, AKT3, ALK1, ALK2, ALK3, ALK4, Aurora A, Aurora B, Aurora C, CHK1, CHK2, CLK1, CLK2, CLK3, DAPK1, DAPK2, DAPK3, DMPK, ERK1, ERK2, ERK5, GCK, GSK3, HIPK, KHS1, LKB1, LOK, MAPKAPK2, MAPKAPK, MNK1, MSSK1, MST1, MST2, MST4, NDR, NEK2, NEK3, NEK6, NEK7, NEK9, NEK11, PAK1, PAK2, PAK3, PAK4, PAK5, PAK6, PIM1, PIM2, PLK1, RIP2, RIP5, RSK1, RSK2, SGK2, SGK3, SIK1, STK33, TAO1, TAO2, TGF-beta, TLK2, TSSK1, TSSK2, ULK1, or ULK2).

In certain embodiments, the Target Protein is derived from a kinase to which the Targeting Ligand is capable of binding or binds including, but not limited to a cyclin dependent kinase for example CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, or CDK13.

In certain embodiments, the Target Protein is derived from a kinase to which the Targeting Ligand is capable of binding or binds including, but not limited to a leucine-rich repeat kinase (e.g., LRRK2).

In certain embodiments, the Target Protein is derived from a kinase to which the Targeting Ligand is capable of binding or binds including, but not limited to a lipid kinase (e.g., PIK3CA, PIK3CB) or a sphingosine kinase (e.g. S1P).

In certain embodiments, the Target Protein is derived from a BET bromodomain-containing protein to which the Targeting Ligand is capable of binding or binds including, but not limited to, ASH1L, ATAD2, BAZ1A, BAZ1B, BAZ2A, BAZ2B, BRD1, BRD2, BRD3, BRD4, BRD5, BRD6, BRD7, BRD8, BRD9, BRD10, BRDT, BRPF1, BRPF3, BRWD3, CECR2, CREBBP, EP300, FALZ, GCN5L2, KIAA1240, LOC93349, MLL, PB1, PCAF, PHIP, PRKCBP1, SMARCA2, SMARCA4, SP100, SP110, SP140, TAF1, TAF1L, TIFla, TRIM28, TRIM33, TRIM66, WDR9, ZMYND11, and MLL4. In certain embodiments, a BET bromodomain-containing protein is BRD4.

In certain embodiments, the Target Protein is derived from a nuclear protein to which the Targeting Ligand is capable of binding or binds including, but not limited to, BRD2, BRD3, BRD4, Antennapedia Homeodomain Protein, BRCA1, BRCA2, CCAAT-Enhanced-Binding Proteins, histones, Polycomb-group proteins, High Mobility Group Proteins, Telomere Binding Proteins, FANCA, FANCD2, FANCE, FANCF, hepatocyte nuclear factors, Mad2, NF-kappa B, Nuclear Receptor Coactivators, CREB-binding protein, p55, p107, p130, Rb proteins, p53, c-fos, c-jun, c-mdm2, c-myc, and c-rel.

In certain embodiments, the Target Protein is a member of the Retinoid X Receptor (RXR) family and the disorder treated is a neuropsychiatric or neurodegenerative disorder. In certain embodiments, the Target Protein is a member of the Retinoid X Receptor (RXR) family and the disorder treated is schizophrenia.

In certain embodiments, the Target Protein is dihydrofolate reductase (DHFR) and the disorder treated is cancer. In certain embodiments, the Target Protein is dihydrofolate reductase (DHFR) and the disorder treated is microbial.

In certain embodiments, the Target Protein is dihydrofolate reductase from *Bacillus anthracis* (BaDHFR) and the disorder treated is anthrax.

In certain embodiments, the Target Protein is Heat Shock Protein 90 (HSP90) and the disorder treated is cancer.

In certain embodiments, the Target Protein is a kinase or phosphatase and the disorder treated is cancer.

In certain embodiments, the Target Protein is HDM2 and or MDM2 and the disorder treated is cancer.

In certain embodiments, the Target Protein is a BET bromodomain containing protein and the disorder treated is cancer.

In certain embodiments, the Target Protein is a lysine methyltransferase and the disorder treated is cancer.

In certain embodiments, the Target Protein belongs to the RAF family and the disorder treated is cancer.

In certain embodiments, the Target Protein belongs to the FKBP family and the disorder treated is an autoimmune disorder. In certain embodiments, the Target Protein belongs to the FKBP family and the disorder treated is organ rejection. In certain embodiments, the Target Protein belongs to the FKBP family and the compound is given prophylactically to prevent organ failure.

In certain embodiments, the Target Protein is an androgen receptor and the disorder treated is cancer.

In certain embodiments, the Target Protein is an estrogen receptor and the disorder treated is cancer.

In certain embodiments, the Target Protein is a viral protein and the disorder treated is a viral infection. In certain embodiments, the Target Protein is a viral protein and the disorder treated is HIV, HPV, HBV, or HCV.

In certain embodiments, the Target Protein is an AP-1 or AP-2 transcription factor and the disorder treated is cancer.

In certain embodiments, the Target Protein is a HIV protease and the disorder treated is a HIV infection. In certain embodiments, the Target Protein is a HIV integrase and the disorder treated is a HIV infection. In certain embodiments, the Target Protein is a HCV protease and the disorder treated is a HCV infection. In certain embodiments, the treatment is prophylactic and the Target Protein is a viral protein.

In certain embodiments, the Target Protein is a member of the histone deacetylase (HDAC) family and the disorder is a neurodegenerative disorder. In certain embodiments, the Target Protein is a member of the histone deacetylase (HDAC) family and the disorder is Huntingon's, Parkinson's, Kennedy disease, amyotropic lateral sclerosis, Rubinstein-Taybi syndrome, or stroke.

In certain embodiments, the Target Protein as referred to herein is named by the gene that expresses it. The person skilled in the art will recognize that when a gene is referred to as a Target Protein, the protein encoded by the gene is the Target Protein. For example, ligands for the protein SMCA2 which is encoded by SMRCA2 are referred to as SMRCA2 Targeting Ligands.

Targeting Ligands

In certain aspects, the Targeting Ligand is a ligand which binds to a Target Protein which has been selected for proteasomal degradation by the selected Degronimer. Non-limiting examples of Targeting Ligands are provided in FIGS. **1A-8**PPPPP, wherein R is the point of attachment to the Linker (which is attached to the Degron).

In one embodiment, the Targeting Ligand binds to an endogenous protein which has been selected for degradation as a means to achieve a therapeutic effect on the host. Illustrative Targeting Ligands include: RXR ligands, DHFR ligands, Hsp90 inhibitors, kinase inhibitors, HDM2 and MDM2 inhibitors, compounds targeting Human BET bromodomain-containing proteins, HDAC inhibitors, ligands of MerTK, ligands of IDH1, ligands of Mcl-1, ligands of SMRCA2, ligands of EGFR, ligands of RAF, ligands of cRAF, human lysine methyltransferase inhibitors, angiogenesis inhibitors, nuclear hormone receptor compounds, immunosuppressive compounds, and compounds targeting the aryl hydrocarbon receptor (AHR), among numerous others. Targeting Ligands also considered to include their pharmaceutically acceptable salts, prodrugs and isotopic derivatives.

In certain aspects, the Targeting Ligand binds to a dehalogenase enzyme in a patient or subject or in a diagnostic assay and is a haloalkane (preferably a C_1-C_{10} alkyl group which is substituted with at least one halo group, preferably a halo group at the distal end of the alkyl group (i.e., away from the Linker). In still other embodiments, the Targeting Ligand is a haloalkyl group, wherein said alkyl group generally ranges in size from about 1 or 2 carbons to about 12 carbons in length, often about 2 to 10 carbons in length, often about 3 carbons to about 8 carbons in length, more often about 4 carbons to about 6 carbons in length. The haloalkyl groups are generally linear alkyl groups (although branched-chain alkyl groups may also be used) and are end-capped with at least one halogen group, preferably a single halogen group, often a single chloride group. Haloalkyl PT, groups for use in the present invention are preferably represented by the chemical structure —$(CH_2)_v$-Halo where v is any integer from 2 to about 12, often about 3 to about 8, more often about 4 to about 6. Halo may be any halogen, but is preferably Cl or Br, more often Cl.

In certain embodiments, the Targeting Ligand is a retinoid X receptor (RXR) agonist or antagonist. Non-limiting examples include retinol, retinoic acid, bexarotene, docosahexenoic acid, compounds disclosed in WO 9929324, the publication by Canan Koch et al. (*J. Med. Chem.* 1996, 39, 3229-3234) titled "Identification of the First Retinoid X Receptor Homodimer Antagonist", WO 9712853, EP 0947496A1, WO 2016002968, and analogs thereof.

In certain embodiments, the Targeting Ligand is a DHFR agonist or antagonist. Non-limiting examples include folic acid, methotrexate, 8,10-dideazatetrahydrofolate compounds disclosed by Tian et al. (Chem. Biol. Drug Des. 2016, 87, 444-454) titled "Synthesis, Antifolate and Anticancer Activities of N5-Substituted 8,10-Dideazatetrahydrofolate Analogues", compounds prepared by Kaur et al. (Biorg. Med. Chem. Lett. 2016, 26, 1936-1940) titled "Rational Modification of the Lead Molecule: Enhancement in the Anticancer and Dihydrofolate Reductase Inhibitory Activity", WO 2016022890, compounds disclosed by Zhang et al. (Int. J. Antimicrob. Agents 46, 174-182) titled "New Small-Molecule Inhibitors of Dihydrofolate Reductase Inhibit *Streptococcus Mutans*", modified trimethoprim analogs developed by Singh et al. (*J. Med. Chem.* 2012, 55, 6381-6390) titled "Mechanism Inspired Development of Rationally Designed Dihydrofolate Reductase Inhibitors as Anticancer Agents", WO20111153310, and analogs thereof.

In certain embodiments, the Targeting Ligand derived from estrogen, an estrogen analog, SERM (selective estrogen receptor modulator), a SERD (selective estrogen receptor degrader), a complete estrogen receptor degrader, or another form of partial or complete estrogen antagonist or agonist. Examples are the partial anti-estrogens raloxifene and tamoxifen and the complete antiestrogen fulvestrant. Non-limiting examples of anti-estrogen compounds are provided in WO 2014/19176 assigned to Astra Zeneca, WO2013/090921, WO 2014/203129, WO 2014/203132, and US2013/0178445 assigned to Olema Pharmaceuticals, and U.S. Pat. Nos. 9,078,871, 8,853,423, and 8,703,810, as well as US 2015/0005286, WO 2014/205136, and WO 2014/205138. Additional non-limiting examples of anti-estrogen compounds include: SERMS such as anordrin, bazedoxifene, broparestriol, chlorotrianisene, clomiphene citrate, cyclofenil, lasofoxifene, ormeloxifene, raloxifene, tamoxifen, toremifene, and fulvestrant; aromatase inhibitors such as aminoglutethimide, testolactone, anastrozole, exemestane, fadrozole, formestane, and letrozole; and antigonadotropins such as leuprorelin, cetrorelix, allylestrenol, chlormadinone acetate, cyproterone acetate, delmadinone acetate, dydrogesterone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, progesterone, and spironolactone. Other estrogenic ligands that can be used according to the present invention are described in U.S. Pat. Nos. 4,418,068; 5,478,847; 5,393,763; and 5,457,117, WO2011/156518, U.S. Pat. Nos. 8,455,534 and 8,299,112, 9,078,871; 8,853,423; 8,703,810; US 2015/0005286; and WO 2014/205138, US2016/0175289, US2015/0258080, WO 2014/191726, WO 2012/084711; WO 2002/013802; WO 2002/004418; WO 2002/003992; WO 2002/003991; WO 2002/003990; WO 2002/003989; WO 2002/003988; WO 2002/003986; WO 2002/003977; WO 2002/003976; WO 2002/003975; WO 2006/078834; U.S. Pat. No. 6,821,989; US 2002/0128276; U.S. Pat. No. 6,777,424; US 2002/0016340; U.S. Pat. Nos. 6,326,392; 6,756,401; US 2002/0013327; U.S. Pat. Nos. 6,512,002; 6,632,834; US 2001/0056099; U.S. Pat. Nos. 6,583,170; 6,479,535; WO 1999/024027; U.S. Pat. No. 6,005,102; EP 0802184; U.S.

Pat. Nos. 5,998,402; 5,780,497, 5,880,137, WO 2012/048058 and WO 2007/087684.

In certain embodiments, the Targeting Ligand is a HSP90 inhibitor identified in Vallee et al. (*J. Med. Chem.* 2011, 54, 7206-7219) titled "Tricyclic Series of Heat Shock Protein 90 (Hsp90) Inhibitors Part I: Discovery of Tricyclic Imidazo [4,5-C]Pyridines as Potent Inhibitors of the Hsp90 Molecular Chaperone", including YKB (N-[4-(3H-imidazo[4,5-C] Pyridin-2-yl)-9H-Fluoren-9-yl]-succinamide), a HSP90 inhibitors (modified) identified in Brough et al. (*J. Med. Chem.* 2008, 51, 196-218) titled "4,5-Diarylisoxazole Hsp90 Chaperone Inhibitors: Potential Therapeutic Agents for the Treatment of Cancer", including compound 2GJ (5-[2,4-dihydroxy-5-(1-methylethyl)phenyl]-n-ethyl-4-[4-(morpholin-4-ylmethyl)phenyl]isoxazole-3-carboxamide), the HSP90 inhibitor geldanamycin ((4E,6Z,8S,9S,10E,12S, 13R,14S,16R)-13-hydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1] (derivatized) or any of its derivatives (e.g. 17-alkylamino-17-desmethoxygeldanamycin ("17-AAG") or 17-(2-dimethylaminoethyl)amino-17-desmethoxygeldanamycin ("17-DMAG")), or a HSP90 inhibitor (modified) identified in Wright et al. (*Chem. Biol.* 2004, 11, 775-785) titled "Structure-Activity Relationships in Purine-Based Inhibitor Binding to Hsp90 Isoforms", including the HSP90 inhibitor PU3. Other non-limiting examples of Hsp90 Targeting Ligands include SNX5422 currently in phase I clinical trials Reddy et al. (*Clin. Lymphoma Myeloma Leuk.* 2013, 13, 385-391) titled "Phase I Trial of the Hsp90 Inhibitor Pf-04929113 (Snx5422) in Adult Patients with Recurrent, Refractory Hematologic Malignancies", or NVP-AUY922 whose anti-cancer activity was assessed by Jensen et al. (*Breast Cancer Research: BCR* 2008, 10, R33-R33) titled "Nvp-Auy922: A Small Molecule Hsp90 Inhibitor with Potent Antitumor Activity in Preclinical Breast Cancer Models".

In certain embodiments, the Targeting Ligand is a kinase inhibitor identified in Millan et al. (*J. Med. Chem.* 2011, 54, 7797-7814) titled "Design and Synthesis of Inhaled P38 Inhibitors for the Treatment of Chronic Obstructive Pulmonary Disease", including the kinase inhibitors Y1W and Y1X, a kinase inhibitor identified in Schenkel et al. (*J. Med. Chem.* 2011, 54, 8440-8450) titled "Discovery of Potent and Highly Selective Thienopyridine Janus Kinase 2 Inhibitors", including the compounds 6TP and OTP, a kinase inhibitor identified in van Eis et al. (*Biorg. Med. Chem. Lett.* 2011, 21, 7367-7372) titled "2,6-Naphthyridines as Potent and Selective Inhibitors of the Novel Protein Kinase C Isozymes", including the kinase inhibitors 07U and YCF identified in Lountos et al. (*J. Struct. Biol.* 2011, 176, 292-301) titled "Structural Characterization of Inhibitor Complexes with Checkpoint Kinase 2 (Chk2), a Drug Target for Cancer Therapy", including the kinase inhibitors XK9 and NXP, afatinib, fostamatinib, gefitinib, lenvatinib, vandetanib, Gleevec, pazopanib, AT-9283, TAE684, nilotanib, NVP-BSK805, crizotinib, JNJ FMS, foretinib, OSI-027, OSI-930, or OSI-906.

In certain embodiments, the Targeting Ligand is a HDM2/MDM2 inhibitor identified in Vassilev et al. (*Science* 2004, 303, 844-848) titled "In Vivo Activation of the P53 Pathway by Small-Molecule Antagonists of Mdm2", and Schneekloth et al. (*Bioorg. Med. Chem. Lett.* 2008, 18, 5904-5908) titled "Targeted Intracellular Protein Degradation Induced by a Small Molecule: En Route to Chemical Proteomics", including the compounds nutlin-3, nutlin-2, and nutlin-1.

In certain embodiments, the Targeting Ligand is a Human BET Bromodomain Targeting Ligand identified in Filippakopoulos et al. (*Nature* 2010, 468, 1067-1073) titled "Selective Inhibition of Bet Bromodomains" such as JQ1; a ligand identified in Nicodeme et al. (*Nature* 2010, 468, 1119-1123) titled "Suppression of Inflammation by a Synthetic Histone Mimic"; Chung et al. (*J. Med. Chem.* 2011, 54, 3827-3838) titled "Discovery and Characterization of Small Molecule Inhibitors of the Bet Family Bromodomains"; a compound disclosed in Hewings et al. (*J. Med. Chem.* 2011, 54, 6761-6770) titled "3,5-Dimethylisoxazoles Act as Acetyl-Lysine-Mimetic Bromodomain Ligands"; a ligand identified in Dawson et al. (*Nature* 2011, 478, 529-533) titled "Inhibition of Bet Recruitment to Chromatin as an Effective Treatment for MLL-Fusion Leukaemia"; or a ligand identified in the following patent applications US 2015/0256700, US 2015/0148342, WO 2015/074064, WO 2015/067770, WO 2015/022332, WO 2015/015318, and WO 2015/011084.

In certain embodiments, the Targeting Ligand is a HDAC Targeting Ligand identified in Finnin et al. (*Nature* 1999, 401, 188-193) titled "Structures of a Histone Deacetylase Homologue Bound to the Tsa and Saha Inhibitors", or a ligand identified as Formula (I) in PCT WO0222577.

In certain embodiments, the Targeting Ligand is a Human Lysine Methyltransferase ligand identified in Chang et al. (*Nat Struct Mol Biol* 2009, 16, 312-317) titled "Structural Basis for G9a-Like Protein Lysine Methyltransferase Inhibition by Bix-01294", a ligand identified in Liu et al. (*J Med Chem* 2009, 52, 7950-7953) titled "Discovery of a 2,4-Diamino-7-Aminoalkoxyquinazoline as a Potent and Selective Inhibitor of Histone Lysine Methyltransferase G9a", azacitidine, decitabine, or an analog thereof.

In certain embodiments, the Targeting Ligand is an angiogenesis inhibitor. Non-limiting examples of angiogenesis inhibitors include: GA-1, estradiol, testosterone, ovalicin, fumagillin, and analogs thereof.

In certain embodiments, the Targeting Ligand is an immunosuppressive compound. Non-limiting examples of immunosuppressive compounds include: AP21998, hydrocortisone, prednisone, prednisolone, methylprednisolone, beclometasone dipropionate, methotrexate, ciclosporin, tacrolimus, actinomycin, and analogues thereof.

In certain embodiments, the Targeting Ligand is an Aryl Hydrocarbon Receptor (AHR) ligand. Non-limiting examples of AHR ligands include: apigenin, SR1, LGC006, and analogues thereof.

In certain embodiments, the Targeting Ligand is a MerTK or Mer Targeting ligand. Non-limiting examples of MerTK Targeting Ligands are included in WO2013/177168 and WO2014/085225, both titled "Pyrimidine Compounds for the Treatment of Cancer" filed by Wang, et al.

In certain embodiments, the Targeting Ligand is an EGFR ligand. In certain embodiments the Targeting Ligand is an EGRF ligand selected from Afatinib, Dacomitinib, Neratinib, Poziotinib, and Canertinib, or derivatives thereof.

In certain embodiments, the Targeting Ligand is a FLT3 Ligand. In certain embodiments, the Targeting Ligand is a FLT3 ligand selected from Tandutinib, Lestaurtinib, Sorafenib, Midostaurin, Quizartinib, and Crenolanib.

In certain embodiments, the Targeting Ligand is a RAF inhibitor. In certain embodiments the Targeting Ligand is a RAF inhibitor selected from Dabrafenib, Regorafenib, and Vemurafenib. In certain embodiments the Targeting Ligand is a cRAF inhibitor.

In some embodiments, the Targeting Ligand is an Ubc9 SUMO E2 ligase 5F6D Targeting Ligand including but not limited to those described in "Insights Into the Allosteric

Inhibition of the SUMO E2 Enzyme Ubc9." by Hewitt, W. M., et. al. (2016) Angew. Chem. Int. Ed. Engl. 55: 5703-5707

In another embodiment, the Targeting Ligand is a Tank1 Targeting Ligand including but not limited to those described in "Structure of human tankyrase 1 in complex with small-molecule inhibitors PJ34 and XAV939." Kirby, C. A., Cheung, A., Fazal, A., Shultz, M. D., Stams, T, (2012) Acta Crystallogr., Sect. F 68: 115-118; and "Structure-Efficiency Relationship of [1,2,4]Triazol-3-ylamines as Novel Nicotinamide Isosteres that Inhibit Tankyrases." Shultz, M. D., et al. (2013) J. Med. Chem. 56: 7049-7059.

In another embodiment, the Targeting Ligand is a SH2 domain of pp60 Src Targeting Ligand including but not limited to those described in "Requirements for Specific Binding of Low Affinity Inhibitor Fragments to the SH2 Domain of pp60Src Are Identical to Those for High Affinity Binding of Full Length Inhibitors," Gudrun Lange, et al., J. Med. Chem. 2003, 46, 5184-5195.

In another embodiment, the Targeting Ligand is a Sec7 domain Targeting Ligand including but not limited to those described in "The Lysosomal Protein Saposin B Binds Chloroquine," Huta, B. P., et al., (2016) Chemmedchem 11: 277.

In another embodiment, the Targeting Ligand is a Saposin-B Targeting Ligand including but not limited to those described in "The structure of cytomegalovirus immune modulator UL 141 highlights structural Ig-fold versatility for receptor binding" I. Nemcovicova and D. M. Zajonc Acta Cryst. (2014). D70, 851-862.

In another embodiment, the Targeting Ligand is a Protein S100-A7 2OWS Targeting Ligand including but not limited to those described in "2WOS STRUCTURE OF HUMAN S100A7 IN COMPLEX WITH 2,6 ANS" DOI: 10.2210/pdb2wos/pdb; and "Identification and Characterization of Binding Sites on S100A7, a Participant in Cancer and Inflammation Pathways." Leon, R., Murray, et al., (2009) Biochemistry 48: 10591-10600.

In another embodiment, the Targeting Ligand is a Phospholipase A2 Targeting Ligand including but not limited to those described in "Structure-based design of the first potent and selective inhibitor of human non-pancreatic secretory phospholipase A2 "Schevitz, R. W., et al., Nat. Struct. Biol. 1995, 2, 458-465.

In another embodiment, the Targeting Ligand is a PHIP Targeting Ligand including but not limited to those described in "A Poised Fragment Library Enables Rapid Synthetic Expansion Yielding the First Reported Inhibitors of PHIP(2), an Atypical Bromodomain" Krojer, T.; et al. Chem. Sci. 2016, 7, 2322-2330.

In another embodiment, the Targeting Ligand is a PDZ Targeting Ligand including but not limited to those described in "Discovery of Low-Molecular-Weight Ligands for the AF6 PDZ Domain" Mangesh Joshi, et al. Angew. Chem. Int. Ed. 2006, 45, 3790-3795.

In another embodiment, the Targeting Ligand is a PARP15 Targeting Ligand including but not limited to those described in "Structural Basis for Lack of ADP-ribosyltransferase Activity in Poly(ADP-ribose) Polymerase-13/Zinc Finger Antiviral Protein." Karlberg, T., et al., (2015) J. Biol. Chem. 290: 7336-7344.

In another embodiment, the Targeting Ligand is a PARP14 Targeting Ligand including but not limited to those described in "Discovery of Ligands for ADP-Ribosyltransferases via Docking-Based Virtual Screening." Andersson, C. D., et al., (2012) J. Med. Chem. 55: 7706-7718.; "Family-wide chemical profiling and structural analysis of PARP and tankyrase inhibitors. "Wahlberg, E., et al. (2012) Nat. Biotechnol. 30: 283-288.; "Discovery of Ligands for ADP-Ribosyltransferases via Docking-Based Virtual Screening. "Andersson, C. D., et al. (2012) J. Med. Chem. 55: 7706-7718.

In another embodiment, the Targeting Ligand is a MTH1 Targeting Ligand including but not limited to those described in "MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool" Helge Gad, et. al. Nature, 2014, 508, 215-221.

In another embodiment, the Targeting Ligand is a mPGES-1 Targeting Ligand including but not limited to those described in "Crystal Structures of mPGES-1 Inhibitor Complexes Form a Basis for the Rational Design of Potent Analgesic and Anti-Inflammatory Therapeutics." Luz, J. G., et al., (2015) J. Med. Chem. 58: 4727-4737.

In another embodiment, the Targeting Ligand is a FLAP-5-lipoxygenase-activating protein Targeting Ligand including but not limited to those described in "Crystal structure of inhibitor-bound human 5-lipoxygenase-activating protein, "Ferguson, A. D., McKeever, B. M., Xu, S., Wisniewski, D., Miller, D. K., Yamin, T. T., Spencer, R. H., Chu, L., Ujjainwalla, F., Cunningham, B. R., Evans, J. F., Becker, J. W. (2007) Science 317: 510-512.

In another embodiment, the Targeting Ligand is a FA Binding Protein Targeting Ligand including but not limited to those described in "A Real-World Perspective on Molecular Design." Kuhn, B.; et al. J. Med. Chem. 2016, 59, 4087-4102.

In another embodiment, the Targeting Ligand is a BCL2 Targeting Ligand including but not limited to those described in "ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets." Souers, A. J., et al. (2013) NAT. MED. (N.Y.) 19: 202-208.

In another embodiment, the Targeting Ligand is a NF2L2 Targeting Ligand.

In another embodiment, the Targeting Ligand is a CTNNB 1 Targeting Ligand.

In another embodiment, the Targeting Ligand is a CBLB Targeting Ligand.

In another embodiment, the Targeting Ligand is a BCL6 Targeting Ligand.

In another embodiment, the Targeting Ligand is a RASK Targeting Ligand.

In another embodiment, the Targeting Ligand is a TNIK Targeting Ligand.

In another embodiment, the Targeting Ligand is a MEN1 Targeting Ligand.

In another embodiment, the Targeting Ligand is a PI3Ka Targeting Ligand.

In another embodiment, the Targeting Ligand is a IDO1 Targeting Ligand.

In another embodiment, the Targeting Ligand is a MCL1 Targeting Ligand.

In another embodiment, the Targeting Ligand is a PTPN2 Targeting Ligand.

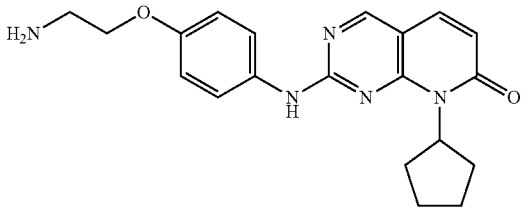
In another embodiment, the Targeting Ligand is a HER2 Targeting Ligand.

In another embodiment, the Targeting Ligand is an EGFR Targeting Ligand. In one embodiment the Targeting Ligand is selected from erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), rociletinib (CO-1686), osimertinib (Tagrisso), olmutinib (Olita), naquotinib (ASP8273), nazartinib (EGF816), PF-06747775 (Pfizer), icotinib (BPI-2009), neratinib (HKI-272; PB272); avitinib (AC0010), EAI045, tarloxotinib (TH-4000; PR-610), PF-06459988 (Pfizer), tesevatinib (XL647; EXEL-7647; KD-019), transtinib,

WZ-3146, WZ8040, CNX-2006, and dacomitinib (PF-00299804; Pfizer). The linker can be placed on these Targeting Ligands in any location that does not interfere with the Ligands binding to EGFR. Non-limiting examples of Linker binding locations are provided in the below tables. In one embodiment, the EGFR Targeting Ligand binds the L858R mutant of EGFR. In another embodiment, the EGFR Targeting Ligand binds the T790M mutant of EGFR. In another embodiment, the EGFR Targeting Ligand binds the $C_{797}G$ or $C_{797}S$ mutant of EGFR. In one embodiment, the EGFR Targeting Ligand is selected from erlotinib, gefitinib, afatinib, neratinib, and dacomitinib and binds the L858R mutant of EGFR. In another embodiment, the EGFR Targeting Ligand is selected from osimertinib, rociletinib, olmutinib, naquotinib, nazartinib, PF-06747775, Icotinib, Neratinib, Avitinib, Tarloxotinib, PF-0645998, Tesevatinib, Transtinib, WZ-3146, WZ8040, and CNX-2006 and binds the T790M mutant of EGFR. In another embodiment, the EGFR Targeting Ligand is EAI045 and binds the C797G or C797S mutant of EGFR.

In one embodiment, the protein target and Targeting Ligand pair are chosen by screening a library of ligands. Such a screening is exemplified in "Kinase Inhibitor Profiling Reveals Unexpected Opportunities to Inhibit Disease-Associated Mutant Kinases" by Duong-Ly et al.; Cell Reports 14, 772-781 Feb. 2, 2016.

In one embodiment, the protein target and Targeting Ligand pair are discovered by screening promiscuous kinase binding ligands for context-specific degradation. Non-limiting examples of targeting ligands are shown below and are found in "Optimized Chemical Proteomics Assay for Kinase Inhibitor Profiling" Guillaume Medard, Fiona Pachl, Benjamin Ruprecht, Susan Klaeger, Stephanie Heinzlmeir, Dominic Helm, Huichao Qiao, Xin Ku, Mathias Wilhelm, Thomas Kuehne, Zhixiang Wu, Antje Dittmann, Carsten Hopf, Karl Kramer, and Bernhard Kuster J. Proteome Res., 2015, 14(3), pp 1574-1586:



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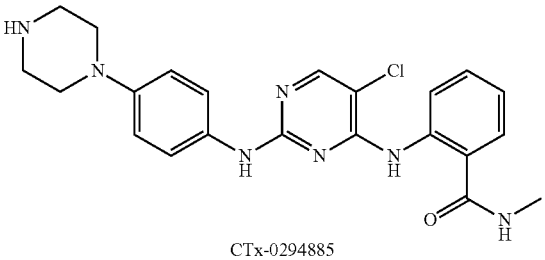

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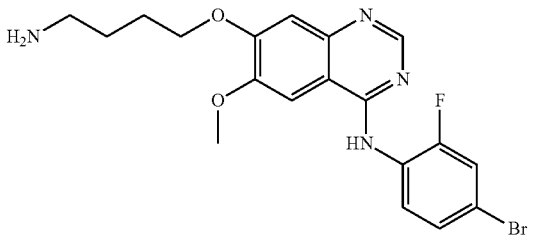
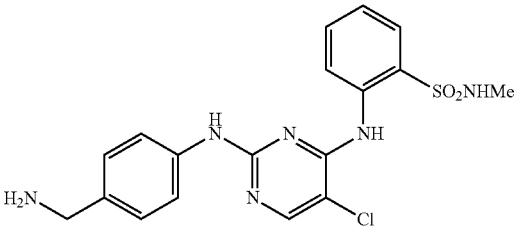


Vandetanib



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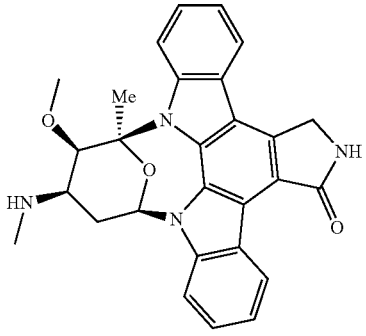
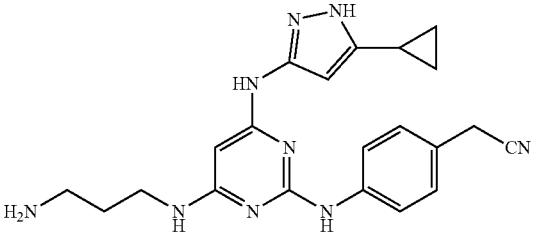


Staurosporine



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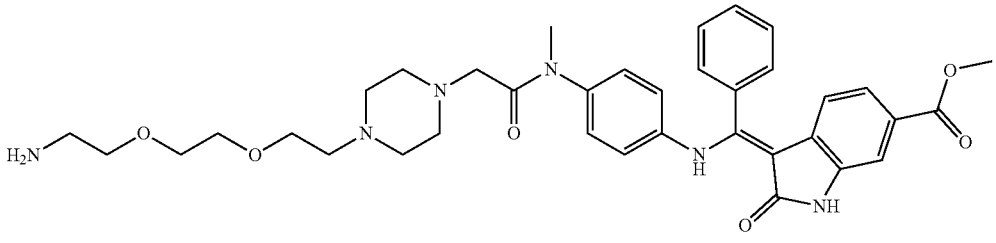

Nintedanib

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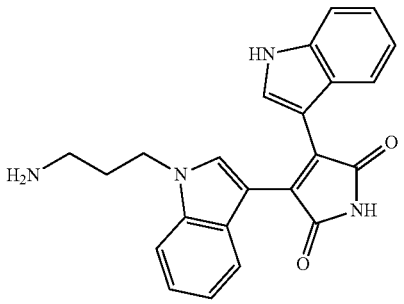

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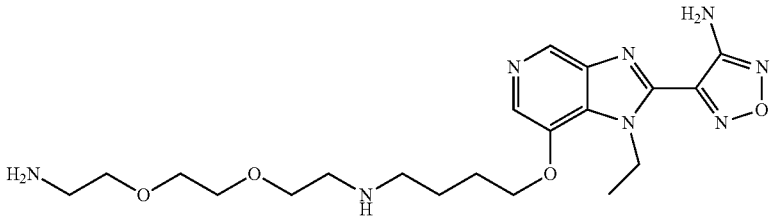

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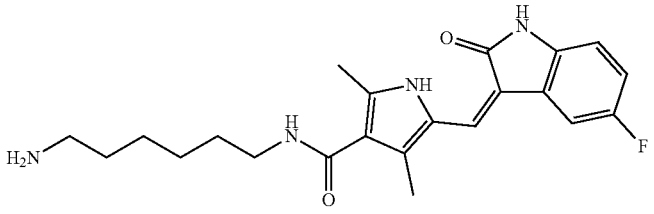

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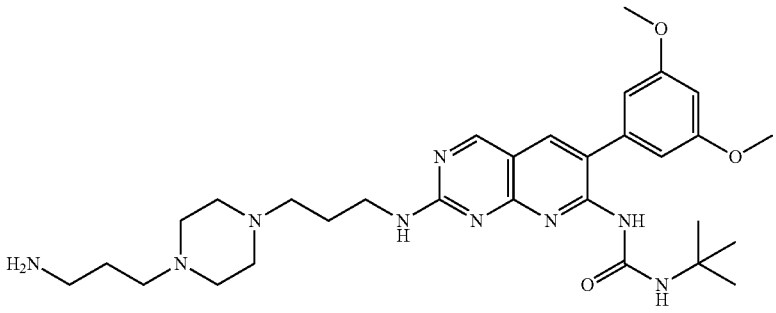

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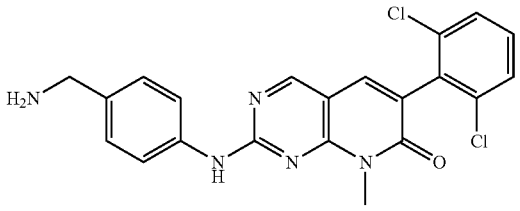

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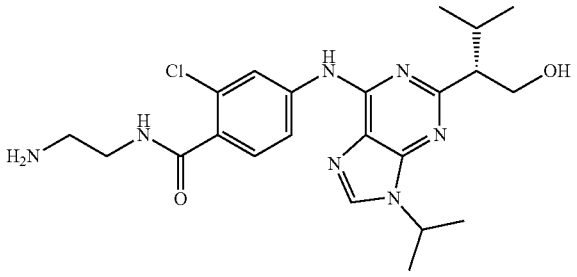
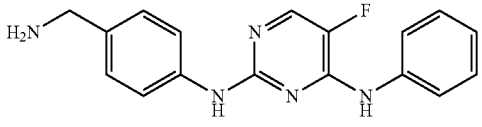
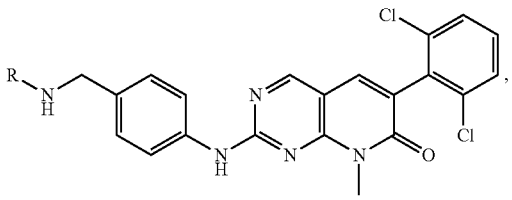


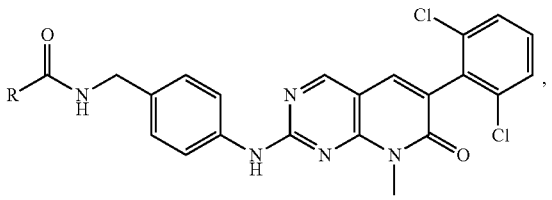
Purvalanol B

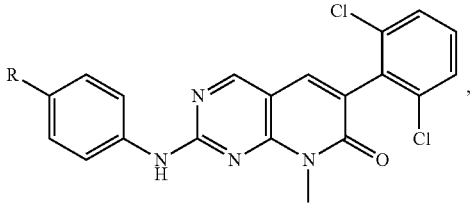


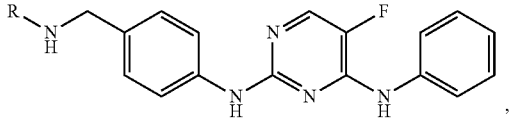
CZC8004

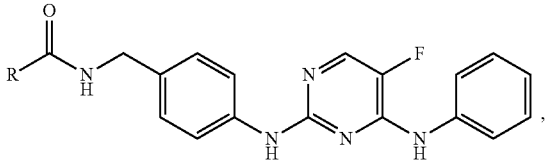
These ligands can be attached to linkers as shown below:

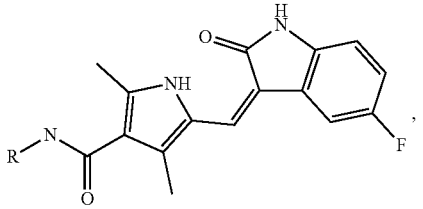


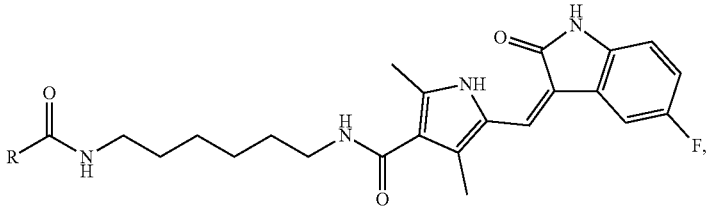


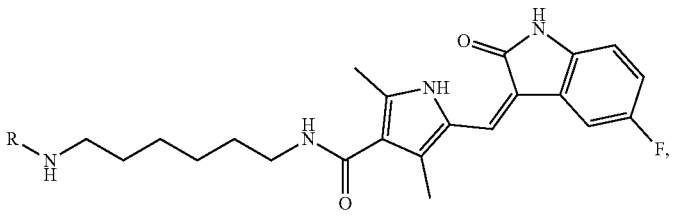


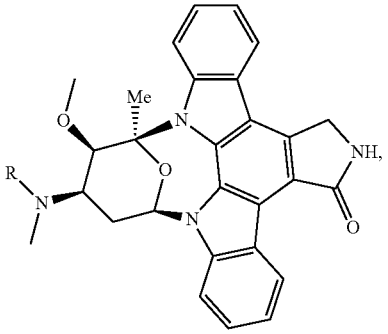


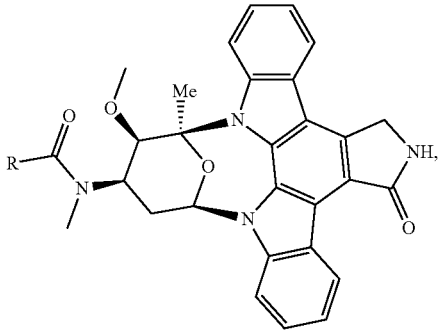


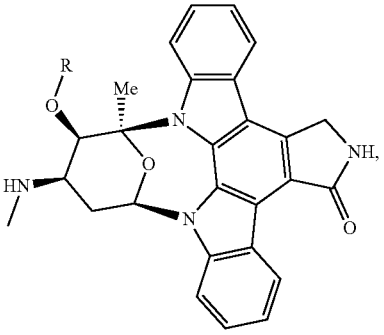












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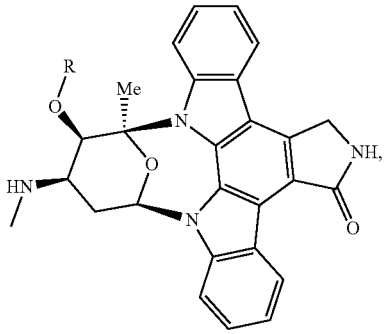

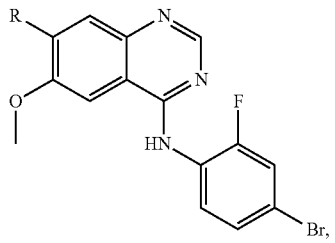

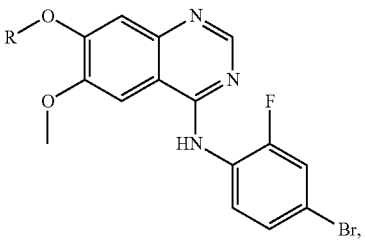

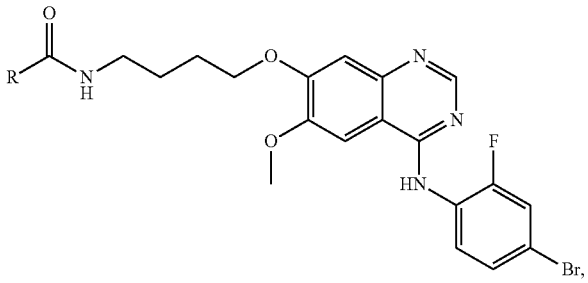

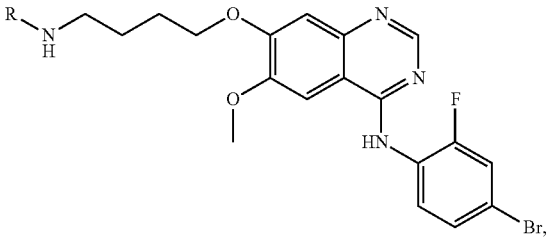

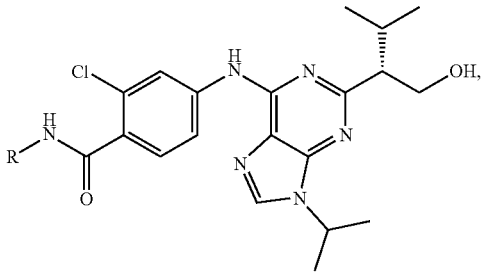

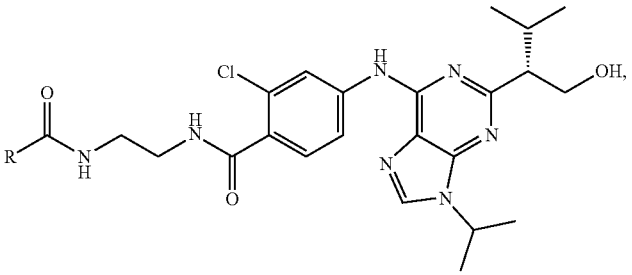

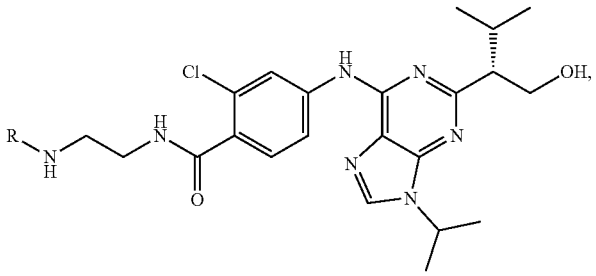

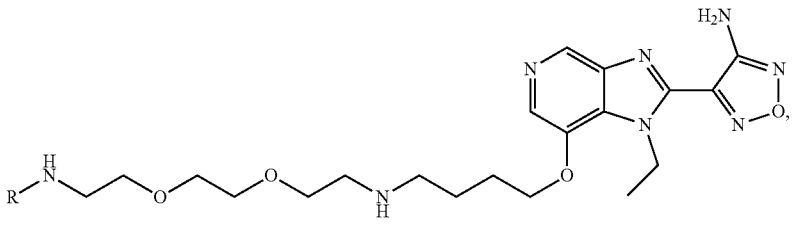

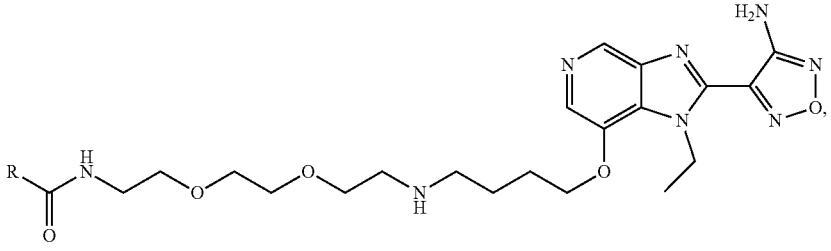

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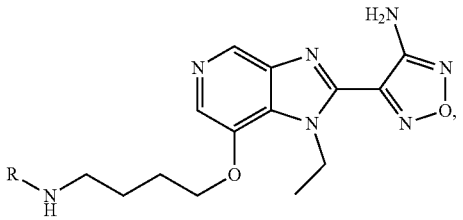

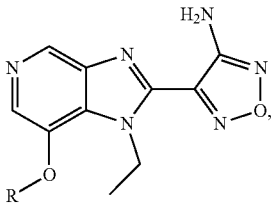

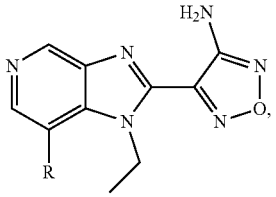

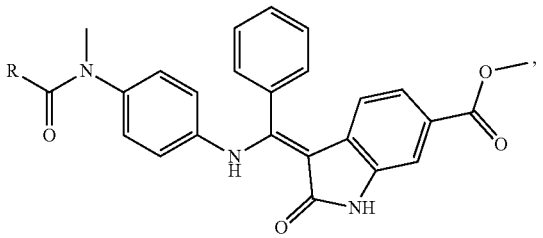

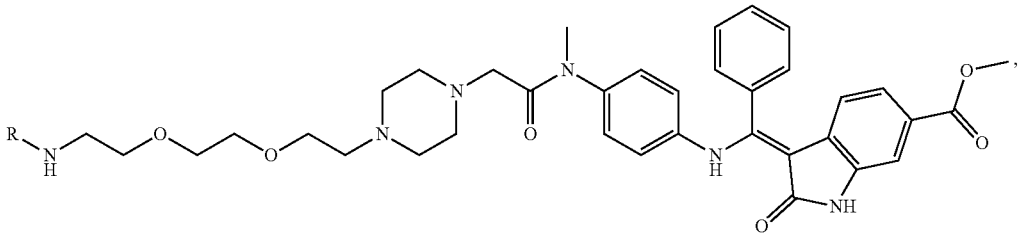

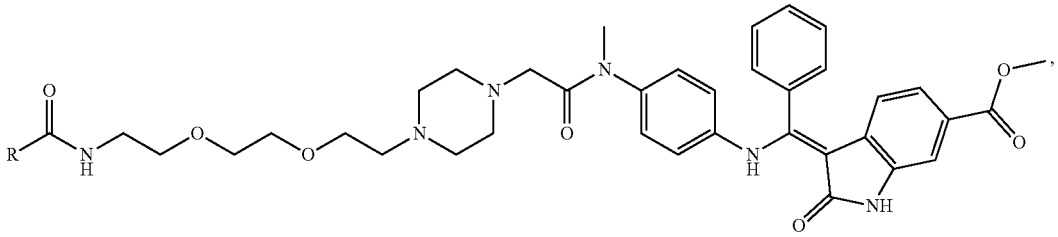

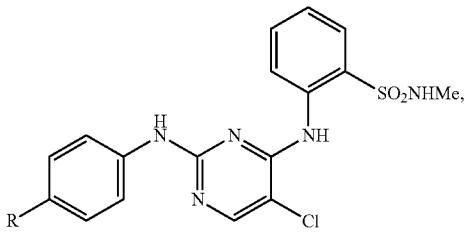

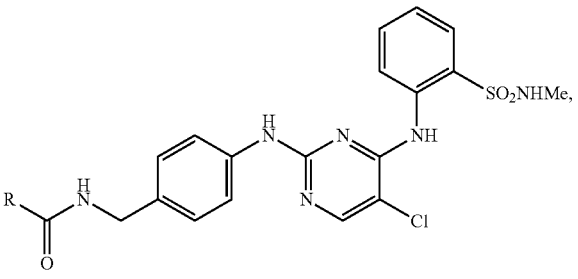

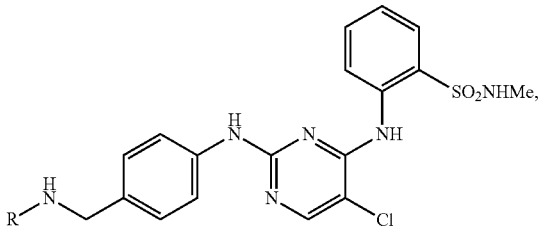

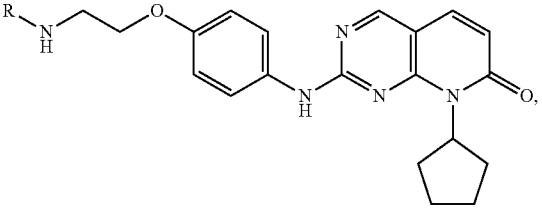

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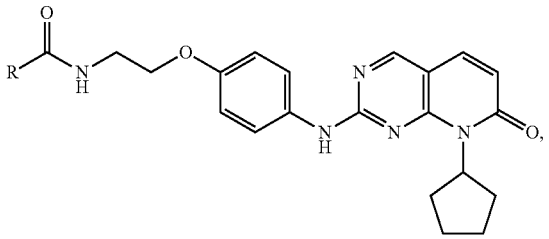

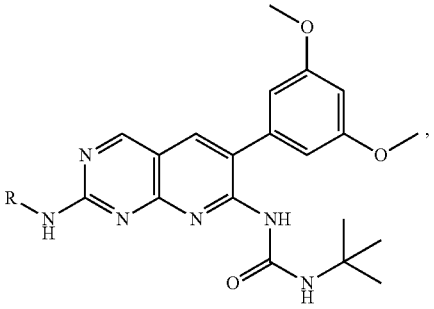

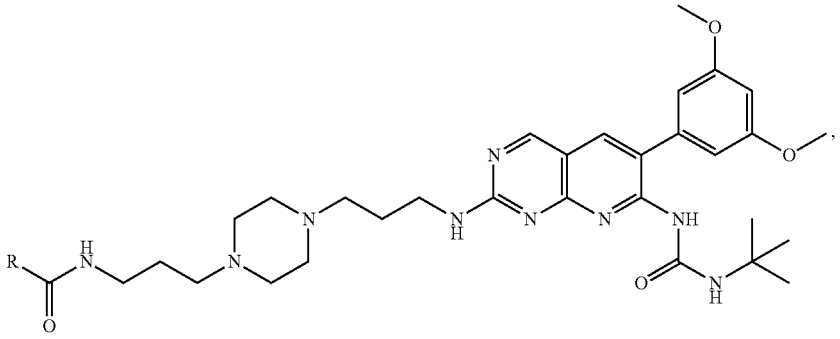

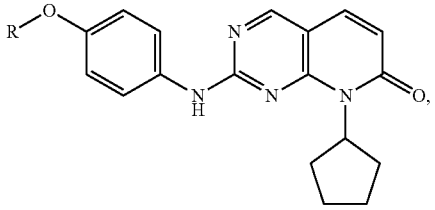

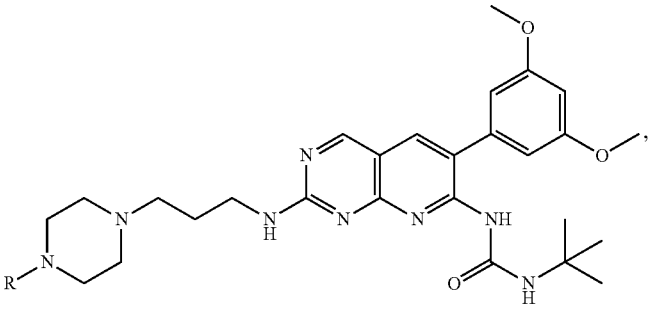

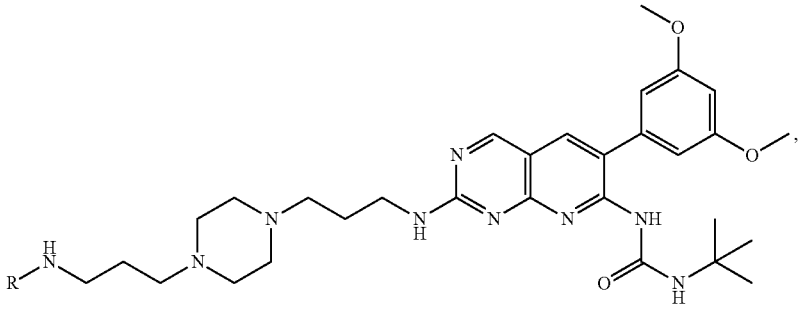

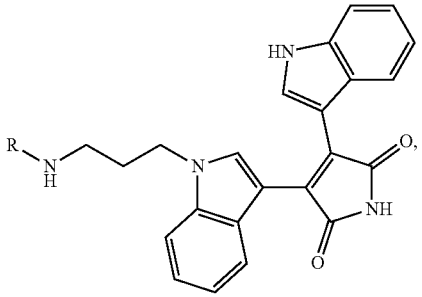

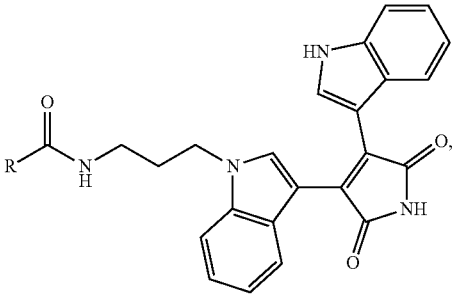

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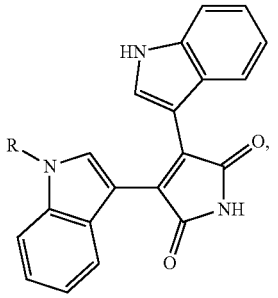
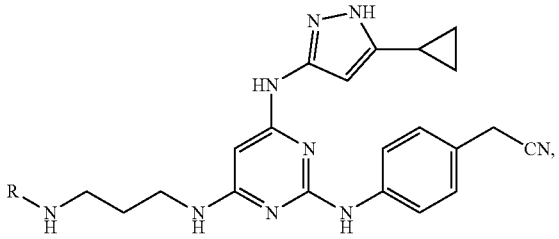
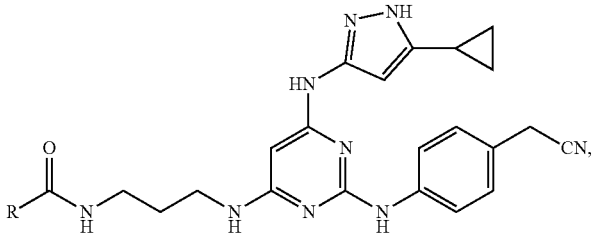
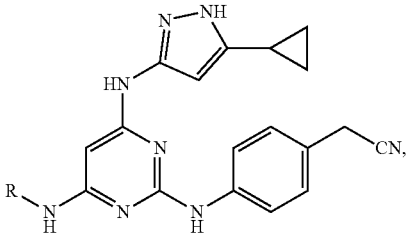
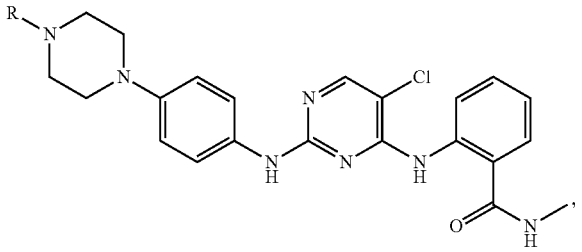
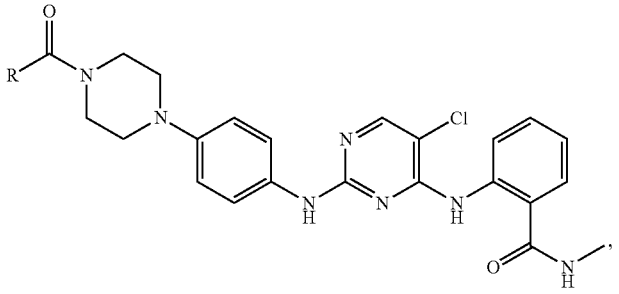


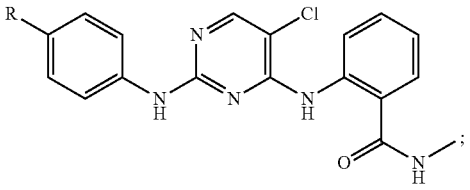












wherein:

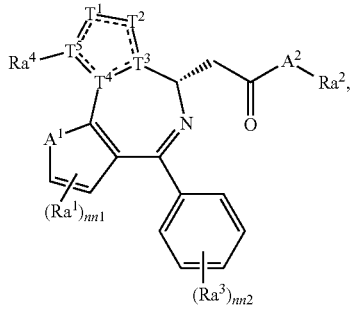
R is the point at which the Linker is attached.

According to the present invention, the Targeting Ligand can be covalently bound to the Linker in any manner that achieves the desired results of the Degronimer for therapeutic use. In certain non-limiting embodiments, the Targeting Ligand is bound to the Linker with a functional group that does not adversely affect the binding of the Ligand to the Target Protein. The attachment points below are exemplary in nature and one of ordinary skill in the art would be able to determine different appropriate attachment points.

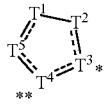
The non-limiting compounds described below exemplify some of the members of these types of Targeting Ligands. In the Tables below, R is the point at which the Linker is attached to the Targeting Ligand.

In certain embodiments, the Targeting Ligand is a compound of Formula TL-I:

(TL-I)



or a pharmaceutically acceptable salt thereof, wherein:



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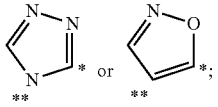


A^1 is S or C═C;

A^2 is NRa^5 or O;

nn1 is 0, 1, or 2;

each Ra^1 is independently C_1-C_3 alkyl, $(CH_2)_{0-3}$—CN, $(CH_2)_{0-3}$-halogen, $(CH_2)_{0-3}$—OH, $(CH_2)_{0-3}$—C_1-C_3 alkoxy, or R;

Ra^2 is H, C_1-C_6 alkyl, $(CH_2)_{0-3}$-heterocyclyl, $(CH_2)_{0-3}$-phenyl, or R, wherein the heterocyclyl comprises one saturated 5- or 6-membered ring and 1-2 heteroatoms selected from N, O, and S and is optionally substituted with C_1-C_3 alkyl and wherein the phenyl is optionally substituted with C_1-C_3 alkyl, CN, halogen, OH, C_1-C_3 alkoxy;

nn2 is 0, 1, 2, or 3;

each Ra^3 is independently C_1-C_3 alkyl, $(CH_2)_{0-3}$—CN, $(CH_2)_{0-3}$-halogen, or R;

Ra^4 is C_1-C_3 alkyl;

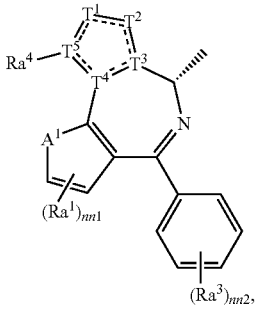
Ra^5 is H or C_1-C_3 alkyl; and

R is the point at which the Linker is attached.

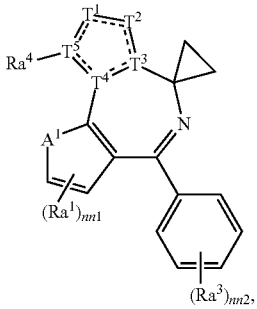
wherein the compound of Formula TL-I is substituted with only one R.

In certain embodiments, the Targeting Ligand is a compound of Formula TL-VIII or Formula TL-IX:

(TL-VIII)



(TL-IX)



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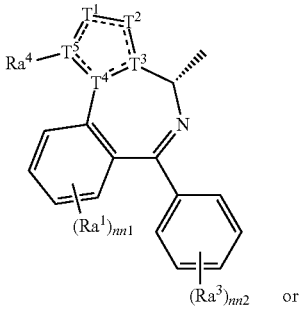
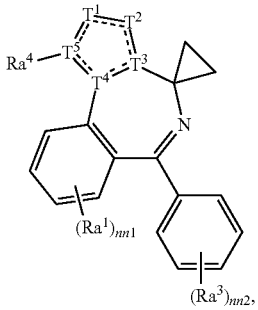
(TL-X)



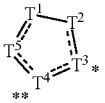
or

(TL-XI)



wherein the compound of Formula TL-VIII or TL-IX is substituted with only one R.

In certain embodiments, is



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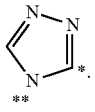
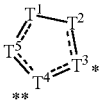
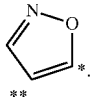


In certain embodiments, is



is



In certain embodiments, A^1 is S.

In certain embodiments, A^1 is C═C.

In certain embodiments, A^2 is NRa^5. In further embodiments, Ra^5 is H. In other embodiments, Ra^5 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In further embodiments, Ra^5 is methyl.

In certain embodiments, A^2 is O.

In certain embodiments, nn1 is 0.

In certain embodiments, nn1 is 1.

In certain embodiments, nn1 is 2.

In certain embodiments, at least one Ra^1 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In further embodiments, at least one Ra^1 is methyl. In further embodiments, two Ra^1 are methyl.

In certain embodiments, at least one Ra^1 is CN, (CH_2)—CN, $(CH_2)_2$—CN, or $(CH_2)_3$—CN. In further embodiments, at least one Ra^1 is (CH_2)—CN.

In certain embodiments, at least one Ra^1 is halogen (e.g., F, Cl, or Br), (CH_2)-halogen, $(CH_2)_2$-halogen, or $(CH_2)_3$-halogen. In further embodiments, at least one Ra^1 is C_1, (CH_2)—C_1, $(CH_2)_2$—Cl, or $(CH_2)_3$—Cl.

In certain embodiments, at least one Ra^1 is OH, (CH_2)—OH, $(CH_2)_2$—OH, or $(CH_2)_3$—OH.

In certain embodiments, at least one Ra^1 is C_1-C_3 alkoxy (e.g., methoxy, ethoxy, or propoxy), (CH_2)—C_1-C_3 alkoxy, $(CH_2)_2$—C_1-C_3 alkoxy, or $(CH_2)_3$—C_1-C_3 alkoxy. In certain embodiments, at least one Ra^1 is methoxy.

In further embodiments, Ra^5 is H. In other embodiments, Ra^5 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl).

In further embodiments, Ra^5 is H. In other embodiments, Ra^5 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In other embodiments, Ra^5 is methyl.

In certain embodiments, one Ra^1 is R.

In certain embodiments, Ra^2 is H.

In certain embodiments, Ra^2 is straight-chain C_1-C_6 or branched C_3-C_6 alkyl (e.g., methyl, ethyl, propyl, i-propyl, butyl, i-butyl, t-butyl, pentyl, or hexyl). In further embodiments, Ra^2 is methyl, ethyl, or t-butyl.

In certain embodiments, Ra^2 is heterocyclyl, (CH_2)-heterocyclyl, $(CH_2)_2$-heterocyclyl, or $(CH_2)_3$-heterocyclyl. In further embodiments, Ra^2 is $(CH_2)_3$-heterocyclyl. In further embodiments, the heterocyclyl is selected from pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, morpholinyl, and thiomorpholinyl. In further embodiments, the heterocyclyl is piperazinyl.

In certain embodiments, the heterocyclyl is substituted with C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl).

In certain embodiments, Ra^2 is phenyl, (CH_2)-phenyl, $(CH_2)_2$-phenyl, or $(CH_2)_3$-phenyl. In further embodiments, Ra^2 is phenyl.

In certain embodiments, the phenyl is substituted with C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In certain embodiments, the phenyl is substituted with CN. In certain embodiments, the phenyl is substituted with halogen (e.g., F, Cl, or Br). In certain embodiments, the phenyl is substituted with OH. In certain embodiments, the phenyl is substituted with C_1-C_3 alkoxy (e.g., methoxy, ethoxy, or propoxy).

In certain embodiments, Ra^2 is R.

In certain embodiments, nn2 is 0.

In certain embodiments, nn2 is 1.

In certain embodiments, nn2 is 2.

In certain embodiments, nn2 is 3.

In certain embodiments, at least one Ra^3 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In further embodiments, at least one Ra^3 is methyl.

In certain embodiments, at least one Ra^3 is CN, (CH_2)—CN, $(CH_2)_2$—CN, or $(CH_2)_3$—CN. In further embodiments, at least one Ra^3 is CN.

In certain embodiments, at least one Ra^3 is halogen (e.g., F, C_1, or Br), (CH_2)-halogen, $(CH_2)_2$-halogen, or $(CH_2)_3$-halogen. In further embodiments, at least one Ra^3 is C_1, (CH_2)—C_1, $(CH_2)_2$—Cl, or $(CH_2)_3$—Cl. In further embodiments, at least one Ra^3 is Cl.

In certain embodiments, one Ra^3 is R.

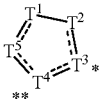
In further embodiments, Ra^5 is H. In other embodiments, Ra^5 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl).

In certain embodiments, Ra^4 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In further embodiments, Ra^4 is methyl.

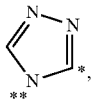
In certain embodiments, Ra^5 is H.

In certain embodiments, Ra^5 is C_1-C_3 alkyl (e.g., methyl, ethyl, propyl, or i-propyl). In further embodiments, Ra^5 is methyl.

In certain embodiments,

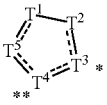


is



and A^1 is S.

In certain embodiments,



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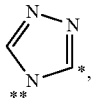
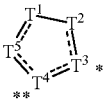


and A^1 is C═C.

In certain embodiments,



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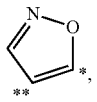


and A^1 is C═C.

In certain embodiments, A^2 is NH, and Ra^2 is $(CH_2)_{0-3}$-heterocyclyl. In further embodiments, Ra^2 is $(CH_2)_3$-heterocyclyl.

In certain embodiments, A^2 is NH, and Ra^2 is $(CH_2)_{0-3}$-phenyl. In further embodiments, Ra^2 is phenyl. In further embodiments, the phenyl is substituted with OH.

In certain embodiments, A^2 is NH, and Ra^2 is R.

In certain embodiments, A^2 is NH, and Ra^2 is H or C_1-C_6 alkyl. In further embodiments, Ra^2 is C_1-C_4 alkyl.

In certain embodiments, A^2 is O, and Ra^2 is H or C_1-C_6 alkyl. In further embodiments, Ra^2 is C_1-C_4 alkyl.

III. Methods of Treatment

The spirocyclic compounds of Formulas I, II, III and IV can be used in an effective amount to treat a host with any of the disorders described herein, including a human, in need thereof, optionally in a pharmaceutically acceptable carrier. In certain embodiments, the method comprises administering an effective amount of the active compound or its salt as described herein, optionally including a pharmaceutically acceptable excipient, carrier, adjuvant, i.e., a pharmaceutically acceptable composition, optionally in combination or alternation with another bioactive agent or combination of agents.

The spirocyclic Degronimer of Formula I and Formula II or a pharmaceutically acceptable salt thereof as described herein can be used to degrade a Target Protein which is a mediator of the disorder affecting the patient, such as a human. The reduction in the Target Protein level afforded by the Formula I or II Degronimers of the present invention provides treatment of the implicated disease state or condition, which is modulated through the Target Protein by lowering the level of that protein in the cell, e.g., cell of a patient. The term "disease state or condition" when used in connection with a Formula I or Formula II compound is meant to refer to any disease state or condition wherein protein dysregulation occurs that involves the selected Target Protein and where degradation of such protein in a patient may provide beneficial therapy or relief of symptoms to a patient in need thereof. In certain instances, the disease state or condition may be cured.

The compounds of Formula I and Formula II are useful as therapeutic agents when administered in an effective amount to a host, including a human, to treat a tumor, cancer (solid, non-solid, diffuse, hematological, etc), abnormal cellular proliferation, immune disorder, inflammatory disorder, blood disorder, a myelo- or lymphoproliferative disorder such as B- or T-cell lymphomas, multiple myeloma, breast cancer, prostate cancer, AML, ALL, ACL, lung cancer, pancreatic cancer, colon cancer, skin cancer, melanoma, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, or a post-transplant lymphoproliferative disorder; an autoimmune disorder, for example, Lupus, Crohn's Disease, Addison disease, Celiac disease, dermatomyositis, Graves disease, thyroiditis, multiple sclerosis, pernicious anemia, reactive arthritis, or type I diabetes; a disease of cardiologic malfunction, including hypercholesterolemia; an infectious disease, including a viral and/or bacterial infection; an inflammatory condition, including asthma, chronic peptic ulcers, tuberculosis, rheumatoid arthritis, periodontitis, ulcerative colitis, or hepatitis.

The term "disease state or condition" when used in connection with a Formula III or Formula IV spirocyclic Degron, for example, refers to any therapeutic indication which can be treated by decreasing the activity of cereblon or a cereblon-containing E3 Ligase, including but not limited to uses known for the cereblon binders thalidomide, pomalidomide or lenalidomide. Nonlimiting examples of uses for cereblon binders are multiple myeloma, a hematological disorder such as myelodysplastic syndrome, cancer, tumor, abnormal cellular proliferation, breast cancer, prostate cancer, AML, ALL, ACL, lung cancer, pancreatic cancer, colon cancer, skin cancer, melanoma, HIV/AIDS, HBV, HCV, hepatitis, Crohn's disease, sarcoidosis, graft-versus-host disease, rheumatoid arthritis, Behcet's disease, tuberculosis, and myelofibrosis. Other indications include a myelo- or lymphoproliferative disorder such as B- or T-cell lymphomas, Waldenstrom's macroglobulinemia, Wiskott-Aldrich syndrome, or a post-transplant lymphoproliferative disorder; an immune disorder, including autoimmune disorders for example as Lupus, Addison disease, Celiac disease, dermatomyositis, Graves disease, thyroiditis, multiple sclerosis, pernicious anemia, arthritis, and in particular rheumatoid arthritis, or type I diabetes; a disease of cardiologic malfunction, including hypercholesterolemia; an infectious disease, including viral and/or bacterial infection, as described generally herein; an inflammatory condition, including asthma, chronic peptic ulcers, tuberculosis, rheumatoid arthritis, periodontitis and ulcerative colitis.

In certain embodiments, the present invention provides the administration of an effective amount of a compound of Formulas I, II, III or IV to treat a patient, for example, a human, having an infectious disease, wherein the therapy targets a Target Protein of the infectious agent (Formulas I and II), or acts via binding to cereblon or its E3 ligase (Formulas III and IV) optionally in combination with another bioactive agent. The disease state or condition may be caused by a microbial agent or other exogenous agent such as a virus (as non-limiting examples, HIV, HBV, HCV, HSV, HPV, RSV, CMV, Ebola, Flavivirus, Pestivirus, Rotavirus, Influenza, Coronavirus, EBV, viral pneumonia, drug-resistant viruses, Bird flu, RNA virus, DNA virus, adenovirus, poxvirus, Picornavirus, Togavirus, Orthomyxovirus, Retrovirus or Hepadnovirus), bacteria (including but not limited to Gram-negative, Gram-positive, Atypical, *Staphylococcus, Streptococcus, E. Coli, Salmonella, Helicobacter pylori*, meningitis, gonorrhea, Chlamydiaceae, Mycoplasmataceae, etc), fungus, protozoa, helminth, worms, prion, parasite, or other microbe.

In certain embodiments, the condition treated with a compound of the present invention is a disorder related to abnormal cellular proliferation. Abnormal cellular proliferation, notably hyperproliferation, can occur as a result of a wide variety of factors, including genetic mutation, infection, exposure to toxins, autoimmune disorders, and benign or malignant tumor induction.

There are a number of skin disorders associated with cellular hyperproliferation. Psoriasis, for example, is a benign disease of human skin generally characterized by plaques covered by thickened scales. The disease is caused by increased proliferation of epidermal cells of unknown cause. Chronic eczema is also associated with significant hyperproliferation of the epidermis. Other diseases caused

by hyperproliferation of skin cells include atopic dermatitis, lichen planus, warts, pemphigus vulgaris, actinic keratosis, basal cell carcinoma and squamous cell carcinoma.

Other hyperproliferative cell disorders include blood vessel proliferation disorders, fibrotic disorders, autoimmune disorders, graft-versus-host rejection, tumors and cancers.

Blood vessel proliferative disorders include angiogenic and vasculogenic disorders. Proliferation of smooth muscle cells in the course of development of plaques in vascular tissue cause, for example, restenosis, retinopathies and atherosclerosis. Both cell migration and cell proliferation play a role in the formation of atherosclerotic lesions.

Fibrotic disorders are often due to the abnormal formation of an extracellular matrix. Examples of fibrotic disorders include hepatic cirrhosis and mesangial proliferative cell disorders. Hepatic cirrhosis is characterized by the increase in extracellular matrix constituents resulting in the formation of a hepatic scar. Hepatic cirrhosis can cause diseases such as cirrhosis of the liver. An increased extracellular matrix resulting in a hepatic scar can also be caused by viral infection such as hepatitis. Lipocytes appear to play a major role in hepatic cirrhosis.

Mesangial disorders are brought about by abnormal proliferation of mesangial cells. Mesangial hyperproliferative cell disorders include various human renal diseases, such as glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic micro-angiopathy syndromes, transplant rejection, and glomerulopathies.

Another disease with a proliferative component is rheumatoid arthritis. Rheumatoid arthritis is generally considered an autoimmune disease that is thought to be associated with activity of autoreactive T cells, and to be caused by autoantibodies produced against collagen and IgE.

Other disorders that can include an abnormal cellular proliferative component include Bechet's syndrome, acute respiratory distress syndrome (ARDS), ischemic heart disease, post-dialysis syndrome, leukemia, acquired immune deficiency syndrome, vasculitis, lipid histiocytosis, septic shock and inflammation in general.

Cutaneous contact hypersensitivity and asthma are just two examples of immune responses that can be associated with significant morbidity. Others include atopic dermatitis, eczema, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, and drug eruptions. These conditions may result in any one or more of the following symptoms or signs: itching, swelling, redness, blisters, crusting, ulceration, pain, scaling, cracking, hair loss, scarring, or oozing of fluid involving the skin, eye, or mucosal membranes.

In atopic dermatitis, and eczema in general, immunologically mediated leukocyte infiltration (particularly infiltration of mononuclear cells, lymphocytes, neutrophils, and eosinophils) into the skin importantly contributes to the pathogenesis of these diseases. Chronic eczema also is associated with significant hyperproliferation of the epidermis. Immunologically mediated leukocyte infiltration also occurs at sites other than the skin, such as in the airways in asthma and in the tear producing gland of the eye in keratoconjunctivitis sicca.

In one non-limiting embodiment compounds of the present invention are used as topical agents in treating contact dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, and drug eruptions. The novel method may also be useful in reducing the infiltration of skin by malignant leukocytes in diseases such as mycosis fungoides. These compounds can also be used to treat an aqueous-deficient dry eye state (such as immune mediated keratoconjunctivitis) in a patient suffering therefrom, by administering the compound topically to the eye.

Disease states which may be treated according to the present invention include, for example, asthma, autoimmune diseases such as multiple sclerosis, various cancers, ciliopathies, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Angelman syndrome, Canavan disease, Coeliac disease, Charcot-Marie-Tooth disease, Cystic fibrosis, Duchenne muscular dystrophy, Haemochromatosis, Haemophilia, Klinefelter's syndrome, Neurofibromatosis, Phenylketonuria, Polycystic kidney disease 1 (PKD1) or 2 (PKD2) Prader-Willi syndrome, Sickle-cell disease, Tay-Sachs disease, Turner syndrome.

Further disease states or conditions which may be treated by the disclosed compounds according to the present invention include Alzheimer's disease, Amyotrophic lateral sclerosis (Lou Gehrig's disease), Anorexia nervosa, Anxiety disorder, Atherosclerosis, Attention deficit hyperactivity disorder, Autism, Bipolar disorder, Chronic fatigue syndrome, Chronic obstructive pulmonary disease, Crohn's disease, Coronary heart disease, Dementia, Depression, Diabetes mellitus type 1, Diabetes mellitus type 2, Epilepsy, Guillain-Barre syndrome, Irritable bowel syndrome, Lupus, Metabolic syndrome, Multiple sclerosis, Myocardial infarction, Obesity, Obsessive-compulsive disorder, Panic disorder, Parkinson's disease, Psoriasis, Rheumatoid arthritis, Sarcoidosis, Schizophrenia, Stroke, Thromboangiitis obliterans, Tourette syndrome, Vasculitis.

Still additional disease states or conditions which can be treated by the disclosed compounds according to the present invention include aceruloplasminemia, Achondrogenesis type II, achondroplasia, Acrocephaly, Gaucher disease type 2, acute intermittent *porphyria*, Canavan disease, Adenomatous Polyposis *Coli*, ALA dehydratase deficiency, adenylosuccinate lyase deficiency, Adrenogenital syndrome, Adrenoleukodystrophy, ALA-D *porphyria*, ALA dehydratase deficiency, Alkaptonuria, Alexander disease, Alkaptonuric ochronosis, alpha 1-antitrypsin deficiency, alpha-1 proteinase inhibitor, emphysema, amyotrophic lateral sclerosis Alstrom syndrome, Alexander disease, Amelogenesis imperfecta, ALA dehydratase deficiency, Anderson-Fabry disease, androgen insensitivity syndrome, Anemia Angiokeratoma Corporis Diffusum, Angiomatosis retinae (von Hippel-Lindau disease) Apert syndrome, Arachnodactyly (Marfan syndrome), Stickler syndrome, Arthrochalasis multiplex congenital (Ehlers-Danlos syndrome # arthrochalasia type) ataxia telangiectasia, Rett syndrome, primary pulmonary hypertension, Sandhoff disease, neurofibromatosis type II, Beare-Stevenson cutis gyrata syndrome, Mediterranean fever, familial, Benjamin syndrome, beta-thalassemia, Bilateral Acoustic Neurofibromatosis (neurofibromatosis type II), factor V Leiden thrombophilia, Bloch-Sulzberger syndrome (incontinentia pigmenti), Bloom syndrome, X-linked sideroblastic anemia, Bonnevie-Ullrich syndrome (Turner syndrome), Bourneville disease (tuberous sclerosis), prion dis-

ease, Birt-Hogg-Dube syndrome, Brittle bone disease (osteogenesis imperfecta), Broad Thumb-Hallux syndrome (Rubinstein-Taybi syndrome), Bronze Diabetes/Bronzed Cirrhosis (hemochromatosis), Bulbospinal muscular atrophy (Kennedy's disease), Burger-Grutz syndrome (lipoprotein lipase deficiency), CGD Chronic granulomatous disorder, Campomelic dysplasia, biotinidase deficiency, Cardiomyopathy (Noonan syndrome), Cri du chat, CAVD (congenital absence of the vas deferens), Caylor cardiofacial syndrome (CBAVD), CEP (congenital erythropoietic *porphyria*), cystic fibrosis, congenital hypothyroidism, Chondrodystrophy syndrome (achondroplasia), otospondylomegaepiphyseal dysplasia, Lesch-Nyhan syndrome, galactosemia, Ehlers-Danlos syndrome, Thanatophoric dysplasia, Coffin-Lowry syndrome, Cockayne syndrome, (familial adenomatous polyposis), Congenital erythropoietic *porphyria*, Congenital heart disease, Methemoglobinemia/Congenital methaemoglobinaemia, achondroplasia, X-linked sideroblastic anemia, Connective tissue disease, Conotruncal anomaly face syndrome, Cooley's Anemia (beta-thalassemia), Copper storage disease (Wilson's disease), Copper transport disease (Menkes disease), hereditary coproporphyria, Cowden syndrome, Craniofacial dysarthrosis (Crouzon syndrome), Creutzfeldt-Jakob disease (prion disease), Cockayne syndrome, Cowden syndrome, Curschmann-Batten-Steinert syndrome (myotonic dystrophy), Beare-Stevenson cutis gyrata syndrome, primary hyperoxaluria, spondyloepimetaphyseal dysplasia (Strudwick type), muscular dystrophy, Duchenne and Becker types (DBMD), Usher syndrome, Degenerative nerve diseases including de Grouchy syndrome and Dejerine-Sottas syndrome, developmental disabilities, distal spinal muscular atrophy, type V, androgen insensitivity syndrome, Diffuse Globoid Body Sclerosis (Krabbe disease), Di George's syndrome, Dihydrotestosterone receptor deficiency, androgen insensitivity syndrome, Down syndrome, Dwarfism, erythropoietic protoporphyria Erythroid 5-aminolevulinate synthetase deficiency, Erythropoietic *porphyria*, erythropoietic protoporphyria, erythropoietic uroporphyria, Friedreich's ataxia-familial paroxysmal polyserositis, *porphyria* cutanea *tarda*, familial pressure sensitive neuropathy, primary pulmonary hypertension (PPH), Fibrocystic disease of the pancreas, fragile X syndrome, galactosemia, genetic brain disorders, Giant cell hepatitis (Neonatal hemochromatosis), Gronblad-Strandberg syndrome (pseudoxanthoma elasticum), Gunther disease (congenital erythropoietic *porphyria*), haemochromatosis, Hallgren syndrome, sickle cell anemia, hemophilia, hepatoerythropoietic *porphyria* (HEP), Hippel-Lindau disease (von Hippel-Lindau disease), Huntington's disease, Hutchinson-Gilford progeria syndrome (progeria), Hyperandrogenism, Hypochondroplasia, Hypochromic anemia, Immune system disorders, including X-linked severe combined immunodeficiency, Insley-Astley syndrome, Jackson-Weiss syndrome, Joubert syndrome, Lesch-Nyhan syndrome, Jackson-Weiss syndrome, Kidney diseases, including hyperoxaluria, Klinefelter's syndrome, Kniest dysplasia, Lacunar dementia, Langer-Saldino achondrogenesis, ataxia telangiectasia, Lynch syndrome, Lysylhydroxylase deficiency, Machado-Joseph disease, Metabolic disorders, including Kniest dysplasia, Marfan syndrome, Movement disorders, Mowat-Wilson syndrome, cystic fibrosis, Muenke syndrome, Multiple neurofibromatosis, Nance-Insley syndrome, Nance-Sweeney chondrodysplasia, Niemann-Pick disease, Noack syndrome (Pfeiffer syndrome), Osler-Weber-Rendu disease, Peutz-Jeghers syndrome, Polycystic kidney disease, polyostotic fibrous dysplasia (McCune-Albright syndrome), Peutz-Jeghers syndrome, Prader-Labhart-Willi syndrome, hemochromatosis, primary hyperuricemia syndrome (Lesch-Nyhan syndrome), primary pulmonary hypertension, primary senile degenerative dementia, prion disease, progeria (Hutchinson Gilford Progeria Syndrome), progressive chorea, chronic hereditary (Huntington) (Huntington's disease), progressive muscular atrophy, spinal muscular atrophy, propionic acidemia, protoporphyria, proximal myotonic dystrophy, pulmonary arterial hypertension, PXE (pseudoxanthoma elasticum), Rb (retinoblastoma), Recklinghausen disease (neurofibromatosis type I), Recurrent polyserositis, Retinal disorders, Retinoblastoma, Rett syndrome, RFALS type 3, Ricker syndrome, Riley-Day syndrome, Roussy-Levy syndrome, severe achondroplasia with developmental delay and acanthosis *nigricans* (SADDAN), Li-Fraumeni syndrome, sarcoma, breast, leukemia, and adrenal gland (SBLA) syndrome, sclerosis tuberose (tuberous sclerosis), SDAT, SED congenital (spondyloepiphyseal dysplasia congenita), SED Strudwick (spondyloepimetaphyseal dysplasia, Strudwick type), SEDc (spondyloepiphyseal dysplasia congenita) SEMD, Strudwick type (spondyloepimetaphyseal dysplasia, Strudwick type), Shprintzen syndrome, Skin pigmentation disorders, Smith-Lemli-Opitz syndrome, South-African genetic *porphyria* (variegate *porphyria*), infantile-onset ascending hereditary spastic paralysis, Speech and communication disorders, sphingolipidosis, Tay-Sachs disease, spinocerebellar ataxia, Stickler syndrome, stroke, androgen insensitivity syndrome, tetrahydrobiopterin deficiency, beta-thalassemia, Thyroid disease, Tomaculous neuropathy (hereditary neuropathy with liability to pressure palsies).

The term "neoplasia" or "cancer" is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or malignant neoplasm, i.e., abnormal tissue (solid) or cells (non-solid) that grow by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, can metastasize to several sites, are likely to recur after attempted removal and may cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Exemplary cancers which may be treated by the present disclosed compounds either alone or in combination with at least one additional anti-cancer agent include squamous-cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinomas, and renal cell carcinomas, cancer of the bladder, bowel, breast, cervix, colon, esophagus, head, kidney, liver, lung, neck, ovary, pancreas, prostate, and stomach; leukemias; benign and malignant lymphomas, particularly Burkitt's lymphoma and Non-Hodgkin's lymphoma; benign and malignant melanomas; myeloproliferative diseases; sarcomas, including Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma, synovial sarcoma, gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, and Schwannomas; bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, esophageal cancer, pancreatic cancer, stomach cancer, liver cancer, colon cancer, melanoma; carcinosarcoma, Hodg-

kin's disease, Wilms' tumor and teratocarcinomas. Additional cancers which may be treated using the disclosed compounds according to the present invention include, for example, acute granulocytic leukemia, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), adenocarcinoma, adenosarcoma, adrenal cancer, adrenocortical carcinoma, anal cancer, anaplastic astrocytoma, angiosarcoma, appendix cancer, astrocytoma, Basal cell carcinoma, B-Cell lymphoma, bile duct cancer, bladder cancer, bone cancer, bone marrow cancer, bowel cancer, brain cancer, brain stem glioma, breast cancer, triple (estrogen, progesterone and HER-2) negative breast cancer, double negative breast cancer (two of estrogen, progesterone and HER-2 are negative), single negative (one of estrogen, progesterone and HER-2 is negative), estrogen-receptor positive, HER2-negative breast cancer, estrogen receptor-negative breast cancer, estrogen receptor positive breast cancer, metastatic breast cancer, luminal A breast cancer, luminal B breast cancer, Her2-negative breast cancer, HER2-positive or negative breast cancer, progesterone receptor-negative breast cancer, progesterone receptor-positive breast cancer, recurrent breast cancer, carcinoid tumors, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), colon cancer, colorectal cancer, craniopharyngioma, cutaneous lymphoma, cutaneous melanoma, diffuse astrocytoma, ductal carcinoma in situ (DCIS), endometrial cancer, ependymoma, epithelioid sarcoma, esophageal cancer, ewing sarcoma, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrosarcoma, gallbladder cancer, gastric cancer, gastrointestinal cancer, gastrointestinal carcinoid cancer, gastrointestinal stromal tumors (GIST), germ cell tumor glioblastoma multiforme (GBM), glioma, hairy cell leukemia, head and neck cancer, hemangioendothelioma, Hodgkin lymphoma, hypopharyngeal cancer, infiltrating ductal carcinoma (IDC), infiltrating lobular carcinoma (ILC), inflammatory breast cancer (IBC), intestinal Cancer, intrahepatic bile duct cancer, invasive/infiltrating breast cancer, Islet cell cancer, jaw cancer, Kaposi sarcoma, kidney cancer, laryngeal cancer, leiomyosarcoma, leptomeningeal metastases, leukemia, lip cancer, liposarcoma, liver cancer, lobular carcinoma in situ, low-grade astrocytoma, lung cancer, lymph node cancer, lymphoma, male breast cancer, medullary carcinoma, medulloblastoma, melanoma, meningioma, Merkel cell carcinoma, mesenchymal chondrosarcoma, mesenchymous, mesothelioma metastatic breast cancer, metastatic melanoma metastatic squamous neck cancer, mixed gliomas, monodermal teratoma, mouth cancer mucinous carcinoma, mucosal melanoma, multiple myeloma, Mycosis Fungoides, myelodysplastic syndrome, nasal cavity cancer, nasopharyngeal cancer, neck cancer, neuroblastoma, neuroendocrine tumors (NETs), non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oat cell cancer, ocular cancer, ocular melanoma, oligodendroglioma, oral cancer, oral cavity cancer, oropharyngeal cancer, osteogenic sarcoma, osteosarcoma, ovarian cancer, ovarian epithelial cancer ovarian germ cell tumor, ovarian primary peritoneal carcinoma, ovarian sex cord stromal tumor, Paget's disease, pancreatic cancer, papillary carcinoma, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, peripheral nerve cancer, peritoneal cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pineal region tumor, pineoblastoma, pituitary gland cancer, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis cancer, rhabdomyosarcoma, salivary gland cancer, soft tissue sarcoma, bone sarcoma, sarcoma, sinus cancer, skin cancer, small cell lung cancer (SCLC), small intestine cancer, spinal cancer, spinal column cancer, spinal cord cancer, squamous cell carcinoma, stomach cancer, synovial sarcoma, T-cell lymphoma, testicular cancer, throat cancer, thymoma/thymic carcinoma, thyroid cancer, tongue cancer, tonsil cancer, transitional cell cancer, tubal cancer, tubular carcinoma, undiagnosed cancer, ureteral cancer, urethral cancer, uterine adenocarcinoma, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, T-cell lineage acute lymphoblastic leukemia (T-ALL), T-cell lineage lymphoblastic lymphoma (T-LL), peripheral T-cell lymphoma, Adult T-cell leukemia, Pre-B ALL, Pre-B lymphomas, large B-cell lymphoma, Burkitts lymphoma, B-cell ALL, Philadelphia chromosome positive ALL, Philadelphia chromosome positive CML, juvenile myelomonocytic leukemia (JMML), acute promyelocytic leukemia (a subtype of AML), large granular lymphocytic leukemia, Adult T-cell chronic leukemia, diffuse large B cell lymphoma, follicular lymphoma; Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL); splenic marginal zone lymphoma (SMZL); intravascular large B-cell lymphoma; primary effusion lymphoma; or lymphomatoid granulomatosis; B-cell prolymphocytic leukemia; splenic lymphoma/leukemia, unclassifiable, splenic diffuse red pulp small B-cell lymphoma; lymphoplasmacytic lymphoma; heavy chain diseases, for example, Alpha heavy chain disease, Gamma heavy chain disease, Mu heavy chain disease, plasma cell myeloma, solitary plasmacytoma of bone; extraosseous plasmacytoma; primary cutaneous follicle center lymphoma, T cell/histocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation; Epstein-Barr virus (EBV)+ DLBCL of the elderly; primary mediastinal (thymic) large B-cell lymphoma, primary cutaneous DLBCL, leg type, ALK+ large B-cell lymphoma, plasmablastic lymphoma; large B-cell lymphoma arising in HHV8-associated multicentric, Castleman disease; B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, or B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma.

IV. Combination Therapy

The disclosed compounds of Formula I, Formula II, Formula III and Formula IV can be used in an effective amount alone or in combination with another compound of the present invention or another bioactive agent to treat a host such as a human with a disorder as described herein.

The disclosed compounds described herein can be used in an effective amount alone or in combination with another compound of the present invention or another bioactive agent to treat a host such as a human with a disorder as described herein.

The term "bioactive agent" is used to describe an agent, other than the selected compound according to the present invention, which can be used in combination or alternation with a compound of the present invention to achieve a desired result of therapy. In one embodiment, the compound of the present invention and the bioactive agent are administered in a manner that they are active in vivo during overlapping time periods, for example, have time-period overlapping Cmax, Tmax, AUC or other pharmacokinetic parameter. In another embodiment, the compound of the present invention and the bioactive agent are administered to

a host in need thereof that do not have overlapping pharmacokinetic parameter, however, one has a therapeutic impact on the therapeutic efficacy of the other.

In one aspect of this embodiment, the bioactive agent is an immune modulator, including but not limited to a checkpoint inhibitor, including as non-limiting examples, a PD-1 inhibitor, PD-L1 inhibitor, PD-L2 inhibitor, CTLA-4 inhibitor, LAG-3 inhibitor, TIM-3 inhibitor, V-domain Ig suppressor of T-cell activation (VISTA) inhibitors, small molecule, peptide, nucleotide, or other inhibitor. In certain aspects, the immune modulator is an antibody, such as a monoclonal antibody.

PD-1 inhibitors that blocks the interaction of PD-1 and PD-L1 by binding to the PD-1 receptor, and in turn inhibit immune suppression include, for example, nivolumab (Opdivo), pembrolizumab (Keytruda), pidilizumab, AMP-224 (AstraZeneca and MedImmune), PF-06801591 (Pfizer), MEDI0680 (AstraZeneca), PDR001 (Novartis), REGN2810 (Regeneron), SHR-12-1 (Jiangsu Hengrui Medicine Company and Incyte Corporation), TSR-042 (Tesaro), and the PD-L1/VISTA inhibitor CA-170 (Curis Inc.). PD-L1 inhibitors that block the interaction of PD-1 and PD-L1 by binding to the PD-L1 receptor, and in turn inhibits immune suppression, include for example, atezolizumab (Tecentriq), durvalumab (AstraZeneca and MedImmune), KN035 (Alphamab), and BMS-936559 (Bristol-Myers Squibb). CTLA-4 checkpoint inhibitors that bind to CTLA-4 and inhibits immune suppression include, but are not limited to, ipilimumab, tremelimumab (AstraZeneca and MedImmune), AGEN1884 and AGEN2041 (Agenus). LAG-3 checkpoint inhibitors, include, but are not limited to, BMS-986016 (Bristol-Myers Squibb), GSK2831781 (GlaxoSmithKline), IMP321 (Prima BioMed), LAG525 (Novartis), and the dual PD-1 and LAG-3 inhibitor MGD013 (MacroGenics). An example of a TIM-3 inhibitor is TSR-022 (Tesaro).

In yet another embodiment, one of the active compounds described herein can be administered in an effective amount for the treatment of abnormal tissue of the female reproductive system such as breast, ovarian, endometrial, or uterine cancer, in combination or alternation with an effective amount of an estrogen inhibitor including but not limited to a SERM (selective estrogen receptor modulator), a SERD (selective estrogen receptor degrader), a complete estrogen receptor degrader, or another form of partial or complete estrogen antagonist or agonist. Partial anti-estrogens like raloxifene and tamoxifen retain some estrogen-like effects, including an estrogen-like stimulation of uterine growth, and also, in some cases, an estrogen-like action during breast cancer progression which actually stimulates tumor growth. In contrast, fulvestrant, a complete anti-estrogen, is free of estrogen-like action on the uterus and is effective in tamoxifen-resistant tumors. Non-limiting examples of anti-estrogen compounds are provided in WO 2014/19176 assigned to Astra Zeneca, WO2013/090921, WO 2014/203129, WO 2014/203132, and US2013/0178445 assigned to Olema Pharmaceuticals, and U.S. Pat. Nos. 9,078,871, 8,853,423, and 8,703, 810, as well as US 2015/0005286, WO 2014/205136, and WO 2014/205138. Additional non-limiting examples of anti-estrogen compounds include: SERMS such as anordrin, bazedoxifene, broparestriol, chlorotrianisene, clomiphene citrate, cyclofenil, lasofoxifene, ormeloxifene, raloxifene, tamoxifen, toremifene, and fulvestratnt; aromatase inhibitors such as aminoglutethimide, testolactone, anastrozole, exemestane, fadrozole, formestane, and letrozole; and antigonadotropins such as leuprorelin, cetrorelix, allylestrenol, chloromadinone acetate, cyproterone acetate, delmadinone acetate, dydrogesterone, medroxyprogesterone acetate, megestrol acetate, nomegestrol acetate, norethisterone acetate, progesterone, and spironolactone. Other estrogenic ligands that can be used according to the present invention are described in U.S. Pat. Nos. 4,418,068; 5,478, 847; 5,393,763; and 5,457,117, WO2011/156518, U.S. Pat. Nos. 8,455,534 and 8,299,112, 9,078,871; 8,853,423; 8,703, 810; US 2015/0005286; and WO 2014/205138, US2016/0175289, US2015/0258080, WO 2014/191726, WO 2012/084711; WO 2002/013802; WO 2002/004418; WO 2002/003992; WO 2002/003991; WO 2002/003990; WO 2002/003989; WO 2002/003988; WO 2002/003986; WO 2002/003977; WO 2002/003976; WO 2002/003975; WO 2006/078834; U.S. Pat. No. 6,821,989; US 2002/0128276; U.S. Pat. No. 6,777,424; US 2002/0016340; U.S. Pat. Nos. 6,326, 392; 6,756,401; US 2002/0013327; U.S. Pat. Nos. 6,512, 002; 6,632,834; US 2001/0056099; U.S. Pat. Nos. 6,583, 170; 6,479,535; WO 1999/024027; U.S. Pat. No. 6,005,102; EP 0802184; U.S. Pat. Nos. 5,998,402; 5,780,497, 5,880, 137, WO 2012/048058 and WO 2007/087684.

In another embodiment, an active compounds described herein can be administered in an effective amount for the treatment of abnormal tissue of the male reproductive system such as prostate or testicular cancer, in combination or alternation with an effective amount of an androgen (such as testosterone) inhibitor including but not limited to a selective androgen receptor modulator, a selective androgen receptor degrader, a complete androgen receptor degrader, or another form of partial or complete androgen antagonist. In one embodiment, the prostate or testicular cancer is androgen-resistant. Non-limiting examples of anti-androgen compounds are provided in WO 2011/156518 and U.S. Pat. Nos. 8,455,534 and 8,299,112. Additional non-limiting examples of anti-androgen compounds include: enzalutamide, apalutamide, cyproterone acetate, chlormadinone acetate, spironolactone, canrenone, drospirenone, ketoconazole, topilutamide, abiraterone acetate, and cimetidine.

In one embodiment, the bioactive agent is an ALK inhibitor. Examples of ALK inhibitors include but are not limited to Crizotinib, Alectinib, ceritinib, TAE684 (NVP-TAE684), GSK1838705A, AZD3463, ASP3026, PF-06463922, entrectinib (RXDX-101), and AP26113.

In one embodiment, the bioactive agent is an EGFR inhibitor. Examples of EGFR inhibitors include erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), rociletinib (CO-1686), osimertinib (Tagrisso), olmutinib (Olita), naquotinib (ASP8273), nazartinib (EGF816), PF-06747775 (Pfizer), icotinib (BPI-2009), neratinib (HKI-272; PB272); avitinib (AC0010), EAI045, tarloxotinib (TH-4000; PR-610), PF-06459988 (Pfizer), tesevatinib (XL647; EXEL-7647; KD-019), transtinib, WZ-3146, WZ8040, CNX-2006, and dacomitinib (PF-00299804; Pfizer).

In one embodiment, the bioactive agent is an HER-2 inhibitor. Examples of HER-2 inhibitors include trastuzumab, lapatinib, ado-trastuzumab emtansine, and pertuzumab.

In one embodiment, the bioactive agent is a CD20 inhibitor. Examples of CD_{20} inhibitors include obinutuzumab, rituximab, fatumumab, ibritumomab, tositumomab, and ocrelizumab.

In one embodiment, the bioactive agent is a JAK3 inhibitor. Examples of JAK3 inhibitors include tasocitinib.

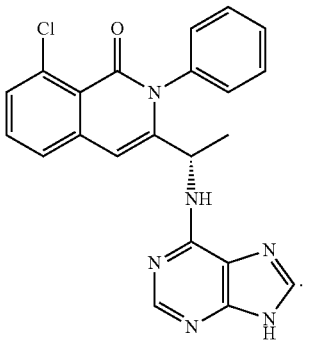
In one embodiment, the bioactive agent is a BCL-2 inhibitor. Examples of BCL-2 inhibitors include venetoclax, ABT-199 (4-[4-[[2-(4-Chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl]piperazin-1-yl]-N-[[3-nitro-4-[[(tetrahydro-2H-pyran-4-yl)methyl]amino]phenyl]sulfonyl]-2-

[(1H-pyrrolo[2,3-b]pyridin-5-yl)oxy]benzamide), ABT-737 (4-[4-[[2-(4-chlorophenyl)phenyl]methyl]piperazin-1-yl]-N-[4-[[(2R)-4-(dimethylamino)-1-phenylsulfanylbutan-2-yl] amino]-3-nitrophenyl]sulfonylbenzamide) (navitoclax), ABT-263 ((R)-4-(4-((4'-chloro-4,4-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-N-((4-((4-morpholino-1-(phenylthio)butan-2-yl)amino)-3((trifluoromethyl)sulfonyl)phenyl)sulfonyl)benzamide), GX15-070 (obatoclax mesylate, (2Z)-2-[(5Z)-5-[(3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-4-methoxypyrrol-2-ylidene]indole; methanesulfonic acid))), 2-methoxy-antimycin A3, YC137 (4-(4,9-dioxo-4,9-dihydronaphtho[2,3-d]thiazol-2-ylamino)-phenyl ester), pogosin, ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate, Nilotinib-d3, TW-37 (N-[4-[[2-(1,1-Dimethylethyl) phenyl] sulfonyl]phenyl]-2,3,4-trihydroxy-5-[[2-(1-methylethyl)phenyl]methyl]benzamide), Apogossypolone (ApoG2), HA14-1, AT101, sabutoclax, gambogic acid, or G3139 (Oblimersen).

In one embodiment, the bioactive agent is a kinase inhibitor. In one embodiment, the kinase inhibitor is selected from a phosphoinositide 3-kinase (PI3K) inhibitor, a Bruton's tyrosine kinase (BTK) inhibitor, or a spleen tyrosine kinase (Syk) inhibitor, or a combination thereof.

Examples of PI3 kinase inhibitors include but are not limited to Wortmannin, demethoxyviridin, perifosine, idelalisib, Pictilisib, Palomid 529, ZSTK474, PWT33597, CUDC-907, and AEZS-136, duvelisib, GS-9820, BKM120, GDC-0032 (Taselisib) (2-[4-[2-(2-Isopropyl-5-methyl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]pyrazol-1-yl]-2-methylpropanamide), MLN-1117 ((2R)-1-Phenoxy-2-butanyl hydrogen (S)-methylphosphonate; or Methyl(oxo) {[(2R)-1-phenoxy-2-butanyl] oxy}phosphonium)), BYL-719 ((2S)—N1-[4-Methyl-5-[2-(2,2,2-trifluoro-1,1-dimethylethyl)-4-pyridinyl]-2-thiazolyl]-1,2-pyrrolidinedicarboxamide), GSK2126458 (2,4-Difluoro-N-{2-(methyloxy)-5-[4-(4-pyridazinyl)-6-quinolinyl]-3-pyridinyl}benzenesulfonamide) (omipalisib), TGX-221 ((±)-7-Methyl-2-(morpholin-4-yl)-9-(1-phenylaminoethyl)-pyrido[1,2-a]-pyrimidin-4-one), GSK2636771 (2-Methyl-1-(2-methyl-3-(trifluoromethyl) benzyl)-6-morpholino-1H-benzo[d]imidazole-4-carboxylic acid dihydrochloride), KIN-193 ((R)-2-((l-(7-methyl-2-morpholino-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl)ethyl) amino)benzoic acid), TGR-1202/RP5264, GS-9820 ((S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-mohydroxypropan-1-one), GS-1101 (5-fluoro-3-phenyl-2-([S])-1-[9H-purin-6-ylamino]-propyl)-3H-quinazolin-4-one), AMG-319, GSK-2269557, SAR245409 (N-(4-(N-(3-((3,5-dimethoxyphenyl)amino)quinoxalin-2-yl)sulfamoyl) phenyl)-3-methoxy-4 methylbenzamide), BAY80-6946 (2-amino-N-(7-methoxy-8-(3-morpholinopropoxy)-2,3-dihydroimidazo[1,2-c]quinaz), AS 252424 (5-[1-[5-(4-Fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione), CZ 24832 (5-(2-amino-8-fluoro-[1,2,4] triazolo[1,5-a]pyridin-6-yl)-N-tert-butylpyridine-3-sulfonamide), Buparlisib (5-[2,6-Di(4-morpholinyl)-4-pyrimidinyl]-4-(trifluoromethyl)-2-pyridinamine), GDC-0941 (2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-4-(4-morpholinyl)thieno[3,2-d] pyrimidine), GDC-0980 ((S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6 yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (also known as RG7422)), SF1126 ((8S,14S,17S)-14-(carboxymethyl)-8-(3-guanidinopropyl)-17-(hydroxymethyl)-3,6,9,12,15-pentaoxo-1-(4-(4-oxo-8-phenyl-4H-chromen-2-yl)morpholino-4-ium)-2-oxa-7,10,13,16-tetraazaoctadecan-18-oate), PF-05212384 (N-[4-[[4-(Dimethylamino)-1-piperidinyl] carbonyl]phenyl]-N'-[4-(4,6-di-4-morpholinyl-1,3,5-triazin-2-yl)phenyl]urea) (gedatolisib), LY3023414, BEZ235 (2-Methyl-2-{4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydro-1H-imidazo[4,5-c]quinolin-1-yl] phenyl}propanenitrile) (dactolisib), XL-765 (N-(3-(N-(3-(3,5-dimethoxyphenylamino)quinoxalin-2-yl)sulfamoyl) phenyl)-3-methoxy-4-methylbenzamide), and GSK1059615 (5-[[4-(4-Pyridinyl)-6-quinolinyl]methylene]-2,4-thiazolidenedione), PX886 ([(3aR,6E,9S,9aR,10R,11aS)-6-[[bis (prop-2-enyl)amino]methylidene]-5-hydroxy-9-(methoxymethyl)-9a,11 a-dimethyl-1,4,7-trioxo-2,3,3a,9,10,11-hexahydroindeno[4,5h]isochromen-10-yl] acetate (also known as sonolisib)), LY294002, AZD8186, PF-4989216, pilaralisib, GNE-317, PI-3065, PI-103, NU7441 (KU-57788), HS 173, VS-5584 (SB2343), CZC24832, TG100-115, A66, YM201636, CAY10505, PIK-75, PIK-93, AS-605240, BGT226 (NVP-BGT226), AZD6482, voxtalisib, alpelisib, IC-87114, TGI100713, CH5132799, PKI-402, copanlisib (BAY 80-6946), XL 147, PIK-90, PIK-293, PIK-294, 3-MA (3-methyladenine), AS-252424, AS-604850, apitolisib (GDC-0980; RG7422), and the structure described in WO2014/071109 having the formula:

Compound 292



Examples of BTK inhibitors include ibrutinib (also known as PCI-32765)(Imbruvica™)(1-[(3R)-3-[4-amino-3-(4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one), dianilinopyrimidine-based inhibitors such as AVL-101 and AVL-291/292 (N-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide) (Avila Therapeutics) (see US Patent Publication No 2011/0117073, incorporated herein in its entirety), Dasatinib ([N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide], LFM-A13 (alpha-cyano-beta-hydroxy-beta-methyl-N-(2,5-ibromophenyl) propenamide), GDC-0834 ([R—N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide], CGI-560 4-(tert-butyl)-N-(3-(8-(phenylamino)imidazo[1,2-a]pyrazin-6-yl) phenyl)benzamide, CGI-1746 (4-(tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide), CNX-774 (4-(4-((4-((3-acrylamidophenyl)amino)-5-fluoropyrimidin-2-yl)amino)phenoxy)-N-methylpicolinamide), CTA056 (7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-g] quinoxalin-6(5H)-one), GDC-0834 ((R)—N-(3-(6-((4-(1,4-

dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), GDC-0837 ((R)—N-(3-(6-((4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide), HM-71224, ACP-196, ONO-4059 (Ono Pharmaceuticals), PRT062607 (4-((3-(2H-1,2,3-triazol-2-yl)phenyl)amino)-2-(((1R,2S)-2-aminocyclohexyl)amino) pyrimidine-5-carboxamide hydrochloride), QL-47 (1-(1-acryloylindolin-6-yl)-9-(1-methyl-1H-pyrazol-4-yl)benzo [h] [1,6]naphthyridin-2(1H)-one), and RN486 (6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2H-isoquinolin-1-one), and other molecules capable of inhibiting BTK activity, for example those BTK inhibitors disclosed in Akinleye et ah, Journal of Hematology & Oncology, 2013, 6:59, the entirety of which is incorporated herein by reference.

Syk inhibitors include, for example, Cerdulatinib (4-(cyclopropylamino)-2-((4-(4-(ethylsulfonyl)piperazin-1-yl) phenyl)amino)pyrimidine-5-carboxamide), entospletinib (6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a] pyrazin-8-amine), fostamatinib ([6-({5-Fluoro-2-[(3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl]methyl dihydrogen phosphate), fostamatinib disodium salt (sodium (6-((5-fluoro-2-((3,4,5-trimethoxyphenyl) amino)pyrimidin-4-yl)amino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl phosphate), BAY 61-3606 (2-(7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino)-nicotinamide HCl), RO9021 (6-[(1R, 2S)-2-Amino-cyclohexylamino]-4-(5,6-dimethyl-pyridin-2-ylamino)-pyridazine-3-carboxylic acid amide), imatinib (Gleevac; 4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl] amino}phenyl)benzamide), staurosporine, GSK143 (2-(((3R,4R)-3-aminotetrahydro-2H-pyran-4-yl)amino)-4-(p-tolylamino)pyrimidine-5-carboxamide), PP2 (1-(tert-butyl)-3-(4-chlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine), PRT-060318 (2-(((1R, 2S)-2-aminocyclohexyl)amino)-4-(m-tolylamino) pyrimidine-5-carboxamide), PRT-062607 (4-((3-(2H-1,2,3-triazol-2-yl)phenyl)amino)-2-(((1R,2S)-2-aminocyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride), R112 (3,3'-((5-fluoropyrimidine-2,4-diyl) bis(azanediyl))diphenol), R348 (3-Ethyl-4-methylpyridine), R406 (6-((5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl)amino)-2,2-dimethyl-2H-pyrido[3,2-b] [1,4] oxazin-3 (4H)-one), piceatannol (3-Hydroxyresveratol), YM193306(see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, *J. Med. Chem.* 2012, 55, 3614-3643), 7-azaindole, piceatannol, ER-27319 (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), Compound D (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), PRT060318 (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), luteolin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), apigenin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), quercetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), fisetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), myricetin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein), morin (see Singh et al. Discovery and Development of Spleen Tyrosine Kinase (SYK) Inhibitors, J. Med. Chem. 2012, 55, 3614-3643 incorporated in its entirety herein).

In one embodiment, the bioactive agent is a MEK inhibitor. MEK inhibitors are well known, and include, for example, trametinib/GSKl120212 (N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6, 8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H-yl}phenyl) acetamide), selumetinib (6-(4-bromo-2-chloroanilino)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSC 1935369 ((S)—N-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino) isonicotinamide), XL-518/GDC-0973 (1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol), refametinib/BAY869766/RDEA1 19 (N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H, 8H)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide), R05126766 (3-[[3-Fluoro-2-(methyl sulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one), WX-554, R04987655/CH4987655 (3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-N-(2 hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide), U0126-EtOH, PD184352 (CI-1040), GDC-0623, BI-847325, cobimetinib, PD98059, BIX 02189, BIX 02188, binimetinib, SL-327, TAK-733, PD318088.

In one embodiment, the bioactive agent is a Raf inhibitor. Raf inhibitors are known and include, for example, Vemurafinib (N-[3-[[5-(4-Chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl]-2,4-difluorophenyl]-1-propanesulfonamide), sorafenib tosylate (4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino]phenoxy]-N-methylpyridine-2-carboxamide; 4-methylbenzenesulfonate), AZ628 (3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-ylamino)phenyl)benzamide), NVP-BHG712 (4-methyl-3-(1-methyl-6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide), RAF-265 (1-methyl-5-[2-[5-(trifluoromethyl)-1H-imidazol-2-yl] pyridin-4-yl]oxy-N-[4-(trifluoromethyl)phenyl] benzimidazol-2-amine), 2-Bromoaldisine (2-Bromo-6,7-dihydro-1H,5H-pyrrolo[2,3-c]azepine-4,8-dione), Raf Kinase Inhibitor IV (2-chloro-5-(2-phenyl-5-(pyridin-4-yl)-1H-imidazol-4-yl)phenol), Sorafenib N-Oxide (4-[4-[[[[4-Chloro-3 (trifluoroMethyl)phenyl] aMino] carbonyl]aMino] phenoxy]-N-Methyl-2pyridinecarboxaMide 1-Oxide), PLX-4720, dabrafenib (GSK2118436), GDC-0879, RAF265, AZ

628, SB590885, ZM336372, GW5074, TAK-632, CEP-32496, LY3009120, and GX818 (Encorafenib).

In one embodiment, the bioactive agent is an AKT inhibitor, including but not limited to, MK-2206, GSK690693, Perifosine, (KRX-0401), GDC-0068, Triciribine, AZD5363, Honokiol, PF-04691502, and Miltefosine, a FLT-3 inhibitor, including but not limited to, P406, Dovitinib, Quizartinib (AC220), Amuvatinib (MP-470), Tandutinib (MLN518), ENMD-2076, and KW-2449, or a combination thereof.

In one embodiment, the bioactive agent is an mTOR inhibitor. Examples of mTOR inhibitors include but are not limited to rapamycin and its analogs, everolimus (Afinitor), temsirolimus, ridaforolimus, sirolimus, and deforolimus. Examples of MEK inhibitors include but are not limited to tametinib/GSKl1120212 (N-(3-{3-Cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6, 8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H-yl}phenyl)acetamide), selumetinob (6-(4-bromo-2-chloroanilino)-7-fluoro-N-(2-hydroxyethoxy)-3-methylbenzimidazole-5-carboxamide), pimasertib/AS703026/MSC 1935369 ((S)—N-(2,3-dihydroxypropyl)-3-((2-fluoro-4-iodophenyl)amino) isonicotinamide), XL-518/GDC-0973 (1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol) (cobimetinib), refametinib/BAY869766/RDEA119 (N-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)-6-methoxyphenyl)-1-(2,3-dihydroxypropyl)cyclopropane-1-sulfonamide), PD-0325901 (N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]-benzamide), TAK733 ((R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3d]pyrimidine-4,7(3H,8H)-dione), MEK162/ARRY438162 (5-[(4-Bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6 carboxamide), R05126766 (3-[[3-Fluoro-2-(methylsulfamoylamino)-4-pyridyl]methyl]-4-methyl-7-pyrimidin-2-yloxychromen-2-one), WX-554, R04987655/$CH_{4987655}$ (3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-5-((3-oxo-1,2-oxazinan-2 yl)methyl)benzamide), or AZD8330 (2-((2-fluoro-4-iodophenyl)amino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide).

In one embodiment, the bioactive agent is a RAS inhibitor. Examples of RAS inhibitors include but are not limited to Reolysin and siG12D LODER.

In one embodiment, the bioactive agent is a HSP inhibitor. HSP inhibitors include but are not limited to Geldanamycin or 17-N-Allylamino-1 7-demethoxygeldanamycin (17AAG), and Radicicol.

Additional bioactive compounds include, for example, everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101, pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111, 131-I-TM-601, ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001, $IPdR_1$ KRX-0402, lucanthone, LY317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311, romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901, AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethyl stilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11, CHIR-258); 3-[5-(methylsulfonylpiperadinemethyl)-indolyl-quinolone, vatalanib, AG-013736, AVE-0005, goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, lonafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951, aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, *Bacillus* Calmette-Guerin (BCG) vaccine, adriamycin, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gleevec, gemcitabine, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291, squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox, gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS-247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001, ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11, dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonist, palonosetron,

aprepitant, diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.

In one embodiment, the bioactive agent is selected from, but are not limited to, Imatinib mesylate (Gleevac®), Dasatinib (Sprycel®), Nilotinib (Tasigna®), Bosutinib (Bosulif®), Trastuzumab (Herceptin®), trastuzumab-DM1, Pertuzumab (Perjeta™), Lapatinib (Tykerb®), Gefitinib (Iressa®), Erlotinib (Tarceva®), Cetuximab (Erbitux®), Panitumumab (Vectibix®), Vandetanib (Caprelsa®), Vemurafenib (Zelboraf®), Vorinostat (Zolinza®), Romidepsin (Istodax®), Bexarotene (Tagretin®), Alitretinoin (Panretin®), Tretinoin (Vesanoid®), Carfilizomib (Kyprolis™), Pralatrexate (Folotyn®), Bevacizumab (Avastin®), Ziv-aflibercept (Zaltrap®), Sorafenib (Nexavar®), Sunitinib (Sutent®), Pazopanib (Votrient®), Regorafenib (Stivarga®), and Cabozantinib (Cometriq™).

In certain aspects, the bioactive agent is an anti-inflammatory agent, a chemotherapeutic agent, a radiotherapeutic, an additional therapeutic agent, or an immunosuppressive agent.

Suitable chemotherapeutic bioactive agents include, but are not limited to, a radioactive molecule, a toxin, also referred to as cytotoxin or cytotoxic agent, which includes any agent that is detrimental to the viability of cells, and liposomes or other vesicles containing chemotherapeutic compounds. General anticancer pharmaceutical agents include: Vincristine (Oncovin®) or liposomal vincristine (Marqibo®), Daunorubicin (daunomycin or Cerubidine®) or doxorubicin (Adriamycin®), Cytarabine (cytosine arabinoside, ara-C, or Cytosar®), L-asparaginase (Elspar®) or PEG-L-asparaginase (pegaspargase or Oncaspar®), Etoposide (VP-16), Teniposide (Vumon®), 6-mercaptopurine (6-MP or Purinethol®), Methotrexate, Cyclophosphamide (Cytoxan®), Prednisone, Dexamethasone (Decadron), imatinib (Gleevec®), dasatinib (Sprycel®), nilotinib (Tasigna®), bosutinib (Bosulif®), and ponatinib (Iclusig™). Examples of additional suitable chemotherapeutic agents include but are not limited to 1-dehydrotestosterone, 5-fluorouracil decarbazine, 6-mercaptopurine, 6-thioguanine, actinomycin D, adriamycin, aldesleukin, an alkylating agent, allopurinol sodium, altretamine, amifostine, anastrozole, anthramycin (AMC)), an anti-mitotic agent, cis-dichlorodiamine platinum (II) (DDP) cisplatin), diamino dichloro platinum, anthracycline, an antibiotic, an antimetabolite, asparaginase, BCG live (intravesical), betamethasone sodium phosphate and betamethasone acetate, bicalutamide, bleomycin sulfate, busulfan, calcium leucouorin, calicheamicin, capecitabine, carboplatin, lomustine (CCNU), carmustine (BSNU), Chlorambucil, Cisplatin, Cladribine, Colchicin, conjugated estrogens, Cyclophosphamide, Cyclothosphamide, Cytarabine, Cytarabine, cytochalasin B, Cytoxan, Dacarbazine, Dactinomycin, dactinomycin (formerly actinomycin), daunirubicin HCL, daunorucbicin citrate, denileukin diftitox, Dexrazoxane, Dibromomannitol, dihydroxy anthracin dione, Docetaxel, dolasetron mesylate, doxorubicin HCL, dronabinol, *E. coli* L-asparaginase, emetine, epoetin-α, *Erwinia* L-asparaginase, esterified estrogens, estradiol, estramustine phosphate sodium, ethidium bromide, ethinyl estradiol, etidronate, etoposide citrororum factor, etoposide phosphate, filgrastim, floxuridine, fluconazole, fludarabine phosphate, fluorouracil, flutamide, folinic acid, gemcitabine HCL, glucocorticoids, goserelin acetate, gramicidin D, granisetron HCL, hydroxyurea, idarubicin HCL, ifosfamide, interferon α-2b, irinotecan HCL, letrozole, leucovorin calcium, leuprolide acetate, levamisole HCL, lidocaine, lomustine, maytansinoid, mechlorethamine HCL, medroxyprogesterone acetate, megestrol acetate, melphalan HCL, mercaptipurine, mesna, methotrexate, methyltestosterone, mithramycin, mitomycin C, mitotane, mitoxantrone, nilutamide, octreotide acetate, ondansetron HCL, paclitaxel, pamidronate disodium, pentostatin, pilocarpine HCL, plimycin, polifeprosan 20 with carmustine implant, porfimer sodium, procaine, procarbazine HCL, propranolol, rituximab, sargramostim, streptozotocin, tamoxifen, taxol, teniposide, tenoposide, testolactone, tetracaine, thioepa chlorambucil, thioguanine, thiotepa, topotecan HCL, toremifene citrate, trastuzumab, tretinoin, valrubicin, vinblastine sulfate, vincristine sulfate, and vinorelbine tartrate.

Additional therapeutic agents that can be administered in combination with a degronimer disclosed herein can include bevacizumab, sutinib, sorafenib, 2-methoxyestradiol or 2ME2, finasunate, vatalanib, vandetanib, aflibercept, volociximab, etaracizumab (MEDI-522), cilengitide, erlotinib, cetuximab, panitumumab, gefitinib, trastuzumab, dovitinib, figitumumab, atacicept, rituximab, alemtuzumab, aldesleukine, atlizumab, tocilizumab, temsirolimus, everolimus, lucatumumab, dacetuzumab, HLL1, huN901-DM1, atiprimod, natalizumab, bortezomib, carfilzomib, marizomib, tanespimycin, saquinavir mesylate, ritonavir, nelfinavir mesylate, indinavir sulfate, belinostat, panobinostat, mapatumumab, lexatumumab, dulanermin, ABT-737, oblimersen, plitidepsin, talmapimod, P276-00, enzastaurin, tipifarnib, perifosine, imatinib, dasatinib, lenalidomide, thalidomide, simvastatin, celecoxib, bazedoxifene, AZD4547, rilotumumab, oxaliplatin (Eloxatin), PD0332991, ribociclib (LEE011), amebaciclib (LY2835219), HDM201, fulvestrant (Faslodex), exemestane (Aromasin), PIM447, ruxolitinib (INC424), BGJ398, necitumumab, pemetrexed (Alimta), and ramucirumab (IMC-1121B).

In one aspect of the invention, the disclosed compound is administered in combination with an anti-infective agent, for example but not limited to an anti-HIV agent, anti-HCV agent, anti-HBV agent, or other anti-viral or anti-bacterial agent. In one embodiment, the anti-HIV agent can be, but is not limited to, for example, a nucleoside reverse transcriptase inhibitor (NRTI), other non-nucloeoside reverse transcriptase inhibitor, protease inhibitor, fusion inhibitor, among others. Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) include, but are not limited to, Abacavir or ABC (Ziagen), Didanosine or ddl (Videx), Emtricitabine or FTC (Emtriva), Lamivudine or 3TC (Epivir), ddC (zalcitabine), Stavudine or d4T (Zerit), Tenofovircor TDF (Viread), D-D4FC (Reverset), and Zidovudine or AZT or ZDV (Retrovir). Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) include, but are not limited to, Delavirdine (Rescriptor), Efavirenz (Sustiva), Etravirine (Intelence), Nevirapine (Viramune), and Rilpivirine (Edurant). Anti-HIV Protease Inhibitors (PIs) include, but are not limited to, Atazanavir or ATV (Reyataz), Darunavir or DRV (Prezista), Fosamprenavir or FPV (Lexiva), Indinavir or IDV (Crixivan), Lopinavir+ritonavir, or LPV/r (Kaletra), Nelfinavir or NFV (Viracept), Ritonavir or RTV (Norvir), Saquinavir or SQV (Invirase), Tipranavir, or TPV (Aptivus), Cobicistat (Tybost), Atazanavir+cobicistat, or ATV/COBI (Evotaz), Darunavir+cobicistat, or DRV/COBI (Prezcobix). Anti-HIV Fusion Inhibitors include, but are not limited to, Enfuvirtide or ENF or T-20 (Fuzeon). Anti-HIV also include, but are not limited to, Maraviroc or MVC (Selzentry). Anti-HIV Integrase Inhibitors include, but are not

limited to Dolutegravir (Tivicay), Elvitegravir (Vitekta), Raltegravir (Isentress). Anti-HIV combinations agents include Abacavir+Dolutegravir+lamivudine, or ABC/DTG/3TC (Triumeq), Abacavir+lamivudine or ABC/3TC (Epzicom), Abacavir+lamivudine+zidovudine, or ABC/3TC/ZDV (Trizivir), Efavirenz+emtricitabine+tenofovir or EFV/FTC/TDF (Atripla, Tribuss), elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide or EVG/COBI/FTC/TAF or ECF/TAF (Genvoya; (Stribild), emtricitabine+rilpivirine+tenofovir or FTC/RPV/TAF (Odefsey); Emtricitabine+rilpivirine+tenofovir or FTC/RPV/TDF (Complera), Emtricitabine+tenofovir or TAF/FTC (Descovy), emtricitabine and tenofovir disoproxil fumarate (Truvada), and Lamivudine+zidovudine or 3TC/ZDV (Combivir). Other anti-HIV compounds include, but are not limited to Racivir, L-FddC, L-FD4C, SQVM (Saquinavir mesylate), IDV (Indinavir), SQV (Saquinavir), APV (Amprenavir), LPV (Lopinavir), fusion inhibitors such as T20, among others, fuseon and mixtures thereof, including anti-HIV compounds presently in clinical trials or in development.

Other anti-HIV agents which may be used in co-administration with the disclosed compounds according to the present invention. NNRTIs may be selected from the group consisting of nevirapine (BI-R6-587), delavirdine (U-90152S/T), efavirenz (DMP-266), UC-781 (N-[4-chloro-3-(3-methyl-2-butenyloxy)phenyl]-2methyl3-furancarbothiamide), etravirine (TMC125), Trovirdine (Ly300046.HCl), HI-236, HI-240, HI-280, HI-281, rilpivirine (TMC-278), MSC-127, HBY 097, DMP266, Baicalin (TJN-151) ADAM-II (Methyl 3',3'-dichloro-4',4"-dimethoxy-5',5"-bis(methoxycarbonyl)-6,6-diphenylhexenoate), Methyl 3-Bromo-5-(1-5-bromo-4-methoxy-3-(methoxycarbonyl)phenyl)hept-1-enyl)-2-methoxybenzoate (Alkenyldiarylmethane analog, Adam analog), (5-chloro-3-(phenylsulfinyl)-2'-indolecarboxamide), AAP-BHAP (U-104489 or PNU-104489), Capravirine (AG-1549, S-1153), atevirdine (U-87201E), aurin tricarboxylic acid (SD-095345), 1-[(6-cyano-2-indolyl)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl]piperazine, 1-[5-[[N-(methyl)methylsulfonylamindo]-2-indolylcarbonyl-4-[3-(isopropylamino)-2-pyridinyl]piperazine, 1-[3-(Ethylamino)-2-[pyridinyl]-4-[(5-hydroxy-2-indolyl)carbonyl]piperazine, 1-[(6-Formyl-2-indolyl)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl] piperazine, 1-[[5-(Methylsulfonyloxy)-2-indoyly)carbonyl]-4-[3-(isopropylamino)-2-pyridinyl]piperazine, U88204E, Bis(2-nitrophenyl)sulfone (NSC 633001), Calanolide A (NSC675451), Calanolide B, 6-Benzyl-5-methyl-2-(cyclohexyloxy)pyrimidin-4-one (DABO-546), DPC 961, E-EBU, E-EBU-dm, E-EPSeU, E-EPU, Foscarnet (Foscavir), HEPT (1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)thymine), HEPT-M (1-[(2-Hydroxyethoxy)methyl]-6-(3-methylphenyl)thio)thymine), HEPT-S(1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-2-thiothymine), Inophyllum P, L-737,126, Michellamine A (NSC650898), Michellamine B (NSC649324), Michellamine F, 6-(3,5-Dimethylbenzyl)-1-[(2-hydroxyethoxy)methyl]-5-isopropyluracil, 6-(3,5-Dimethylbenzyl)-1-(ethyoxymethyl)-5-isopropyluracil, NPPS, E-BPTU (NSC 648400), Oltipraz (4-Methyl-5-(pyrazinyl)-3H-1,2-dithiole-3-thione), N-{2-(2-Chloro-6-fluorophenethyl]-N'-(2-thiazolyl)thiourea (PETT Cl, F derivative), N-{2-(2,6-Difluorophenethyl]-N'-[2-(5-bromopyridyl)]thiourea {PETT derivative), N-{2-(2,6-Difluorophenethyl]-N'-[2-(5-methylpyridyl]thiourea {PETT Pyridyl derivative), N-[2-(3-Fluorofuranyl)ethyl]-N'-[2-(5-chloropyridyl)]thiourea, N-[2-(2-Fluoro-6-ethoxyphenethyl)]-N'-[2-(5-bromopyridyl)]thiourea, N-(2-Phenethyl)-N'-(2-thiazolyl)thiourea (LY-73497), L-697,639, L-697,593, L-697,661, 342-(4,7-Difluorobenzoxazol-2-yl)ethyl}-5-ethyl-6-methyl (pypridin-2(1H)-thione (2-Pyridinone Derivative), 3-[[(2-Methoxy-5,6-dimethyl-3-pyridyl)methyl]amine]-5-ethyl-6-methyl(pypridin-2(1H)-thione, R82150, R82913, R87232, R88703, R89439 (Loviride), R90385, S-2720, Suramin Sodium, TBZ (Thiazolobenzimidazole, NSC 625487), Thiazoloisoindol-5-one, (+)(R)-9b-(3,5-Dimethylphenyl-2,3-dihydrothiazolo[2,3-a]isoindol-5 (9bH)-one, Tivirapine (R86183), UC-38 and UC-84, among others.

In one aspect of the invention, the disclosed compound when used to treat an HCV infection can be administered in combination with another anti-HCV agent. Anti-HCV agents are known in the art. To date, a number of fixed dose drug combinations have been approved for the treatment of HCV. Harvoni® (Gilead Sciences, Inc.) contains the NS5A inhibitor ledipasvir and the NS5B inhibitor sofosbuvir. Technivie™ (AbbVie, Inc.) is a fixed-dose combination containing ombitasvir, an NS5A inhibitor; paritaprevir, an NS3/4A protease inhibitor; and ritonavir, a CYP3A inhibitor. Daklinza™ (daclatasvir, Bristol-Myers Squibb) is a HCV NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic genotype 3 infection. Zepatier™ (Merck & Co.) has recently been approved for the treatment of chronic HCV genotypes 1 and 4. Zepatier™ is a fixed-dose combination product containing elbasvir, an HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor. Zepatier™ is indicated with or without ribavirin. Epclusa® (Gilead Sciences, Inc.) is a fixed-dose combination tablet containing sofosbuvir and velpatasvir. Additional anti-HCV agents and combinations thereof include those described in U.S. Pat. Nos. 9,382,218; 9,321,753; 9,249,176; 9,233,974; 9,221,833; 9,211,315; 9,194,873; 9,186,369; 9,180,193; 9,156,823; 9,138,442; 9,133,170; 9,108,999; 9,090,559; 9,079,887; 9,073,943; 9,073,942; 9,056,090; 9,051,340; 9,034,863; 9,029,413; 9,011,938; 8,987,302; 8,945,584; 8,940,718; 8,927,484; 8,921,341; 8,884,030; 8,841,278; 8,822,430; 8,772,022; 8,765,722; 8,742,101; 8,741,946; 8,674,085; 8,673,288; 8,669,234; 8,663,648; 8,618,275; 8,580,252; 8,575,195; 8,575,135; 8,575,118; 8,569,302; 8,524,764; 8,513,298; 8,501,714; 8,404,651; 8,273,341; 8,257,699; 8,197,861; 8,158,677; 8,105,586; 8,093,353; 8,088,368; 7,897,565; 7,871,607; 7,846,431; 7,829,081; 7,829,077; 7,824,851; 7,572,621; and 7,326,536; Patents assigned to Alios: U.S. Pat. Nos. 9,365,605; 9,346,848; 9,328,119; 9,278,990; 9,249,174; 9,243,022; 9,073,960; 9,012,427; 8,980,865; 8,895,723; 8,877,731; 8,871,737; 8,846,896 and 8,772,474; Achillion U.S. Pat. Nos. 9,273,082; 9,233,136; 9,227,952; 9,133,115; 9,125,904; 9,115,175; 9,085,607; 9,006,423; 8,946,422; 8,835,456; 8,809,313; 8,785,378; 8,614,180; 8,445,430; 8,435,984; 8,183,263; 8,173,636; 8,163,693; 8,138,346; 8,114,888; 8,106,209; 8,088,806; 8,044,204; 7,985,541; 7,906,619; 7,902,365; 7,767,706; 7,741,334; 7,718,671; 7,659,399; 7,476,686; 7,439,374; 7,365,068; 7,199,128; and 7,094,807; Cocrystal Pharma Inc. U.S. Pat. Nos. 9,181,227; 9,173,893; 9,040,479 and 8,771,665; Gilead Sciences U.S. Pat. Nos. 9,353,423; 9,346,841; 9,321,800; 9,296,782; 9,296,777; 9,284,342; 9,238,039; 9,216,996; 9,206,217; 9,161,934; 9,145,441; 9,139,604; 9,090,653; 9,090,642; 9,085,573; 9,062,092; 9,056,860; 9,045,520; 9,045,462; 9,029,534; 8,980,878; 8,969,588; 8,962,652; 8,957,046; 8,957,045; 8,946,238; 8,933,015; 8,927,741; 8,906,880; 8,889,159; 8,871,785; 8,841,275; 8,815,858; 8,809,330; 8,809,267; 8,809,266; 8,779,141; 8,765,710; 8,759,544; 8,759,510; 8,735,569; 8,735,372; 8,729,089; 8,722,677; 8,716,264; 8,716,263; 8,716,262; 8,697,861; 8,664,386; 8,642,756; 8,637,531; 8,633,309; 8,629,263; 8,618,076; 8,592,397;

8,580,765; 8,569,478; 8,563,530; 8,551,973; 8,536,187; 8,513,186; 8,513,184; 8,492,539; 8,486,938; 8,481,713; 8,476,225; 8,420,597; 8,415,322; 8,338,435; 8,334,270; 8,329,926; 8,329,727; 8,324,179; 8,283,442; 8,263,612; 8,232,278; 8,178,491; 8,173,621; 8,163,718; 8,143,394; patents assigned to Idenix, acquired by Merck, include U.S. Pat. Nos. 9,353,100; 9,309,275; 9,296,778; 9,284,307; 9,249,173; 9,243,025; 9,211,300; 9,187,515; 9,187,496, 9,109,001; 8,993,595; 8,951,985; 8,691,788; 8,680,071; 8,637,475; 8,507,460; 8,377,962; 8,362,068; 8,343,937; 8,299,038; 8,193, 372; 8,093,379; 7,951,789; 7,932,240; 7,902,202; 7,662,798; 7,635,689; 7,625,875; 7,608,600; 7,608,597; 7,582,618; 7,547,704; 7,456,155; 7,384,924; 7,365,057; 7,192,936; 7,169,766; 7,163,929; 7,157,441; 7,148,206; 7,138,376; 7,105,493; 6,914,054 and 6,812,219; patents assigned to Merck include U.S. Pat. Nos. 9,364,482; 9,339,541; 9,328,138; 9,265,773; 9,254,292; 9,243,002; 9,242,998; 9,242,988; 9,242,917; 9,238,604; 9,156,872; 9,150,603; 9,139,569; 9,120,818; 9,090,661; 9,073,825; 9,061,041; 8,987,195; 8,980,920; 8,927,569; 8,871,759; 8,828,930; 8,772,505; 8,715,638; 8,697,694; 8,637,449; 8,609,635; 8,557,848; 8,546,420; 8,541,434; 8,481,712; 8,470,834; 8,461,107; 8,404,845; 8,377,874; 8,377,873; 8,354,518; 8,309,540; 8,278,322; 8,216,999; 8,148,349; 8,138,164; 8,080,654; 8,071,568; 7,973,040; 7,935,812; 7,915,400; 7,879,815; 7,879,797; 7,632,821; 7,569,374; 7,534,767; 7,470,664 and 7,329,732; patent application publication US 2013/0029904 to Boehringer Ingelheim GMBH and US 2014/0113958 to Stella Aps.

In one embodiment, the additional therapy is a monoclonal antibody (MAb). Some MAbs stimulate an immune response that destroys cancer cells. Similar to the antibodies produced naturally by B cells, these MAbs may "coat" the cancer cell surface, triggering its destruction by the immune system. For example, bevacizumab targets vascular endothelial growth factor(VEGF), a protein secreted by tumor cells and other cells in the tumor's microenvironment that promotes the development of tumor blood vessels. When bound to bevacizumab, VEGF cannot interact with its cellular receptor, preventing the signaling that leads to the growth of new blood vessels. Similarly, cetuximab and panitumumab target the epidermal growth factor receptor (EGFR), and trastuzumab targets the human epidermal growth factor receptor 2 (HER-2). MAbs that bind to cell surface growth factor receptors prevent the targeted receptors from sending their normal growth-promoting signals. They may also trigger apoptosis and activate the immune system to destroy tumor cells.

In one aspect of the present invention, the bioactive agent is an immunosuppressive agent. The immunosuppressive agent can be a calcineurin inhibitor, e.g. a cyclosporin or an ascomycin, e.g. Cyclosporin A (NEORAL®), FK506 (tacrolimus), pimecrolimus, a mTOR inhibitor, e.g. rapamycin or a derivative thereof, e.g. Sirolimus (RAPAMUNE®), Everolimus (Certican®), temsirolimus, zotarolimus, biolimus-7, biolimus-9, a rapalog, e.g.ridaforolimus, azathioprine, campath 1H, a S1P receptor modulator, e.g. fingolimod or an analogue thereof, an anti IL-8 antibody, mycophenolic acid or a salt thereof, e.g. sodium salt, or a prodrug thereof, e.g. Mycophenolate Mofetil (CELLCEPT®), OKT3 (ORTHOCLONE OKT3®), Prednisone, ATGAM®, THYMOGLOBULIN®, Brequinar Sodium, OKT4, T10B9.A-3A, 33B3.1, 15-deoxyspergualin, tresperimus, Leflunomide ARAVA®, CTLAI-Ig, anti-CD_{25}, anti-IL2R, Basiliximab (SIMULECT®), Daclizumab (ZENAPAX®), mizorbine, methotrexate, dexamethasone, ISAtx-247, SDZ ASM 981 (pimecrolimus, Elidel®), CTLA4lg (Abatacept), belatacept, LFA3lg, etanercept (sold as Enbrel® by Immunex), adalimumab (Humira®), infliximab (Remicade®), an anti-LFA-1 antibody, natalizumab (Antegren®), Enlimomab, gavilimomab, antithymocyte immunoglobulin, siplizumab, Alefacept efalizumab, pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

V. Pharmaceutical Compositions

The compounds of Formula I, Formula II, Formula III and Formula IV, as disclosed herein can be administered as the neat chemical, but are more typically administered as a pharmaceutical composition, that includes an effective amount for a host, typically a human, in need of such treatment for any of the disorders described herein. Accordingly, the disclosure provides pharmaceutical compositions comprising an effective amount of the disclosed compound or pharmaceutically acceptable salt thereof together with at least one pharmaceutically acceptable carrier for any of the uses described herein. The pharmaceutical composition may contain the disclosed compound or salt as the only active agent, or, in an alternative embodiment, the disclosed compound and at least one additional active agent.

Compounds disclosed herein may be administered by any suitable route desired by the healthcare provider, including orally, topically, systemically, parenterally, by inhalation or spray, sublingually, via implant, including ocular implant, transdermally, via buccal administration, rectally, as an ophthalmic solution, injection, including ocular injection, intraveneous, intra-arterial, intra-aortal, intracranial, subdermal, intraperitioneal, subcutaneous, transnasal, sublingual, or rectal or by other means, in dosage unit formulations containing conventional pharmaceutically acceptable carriers.

In general, the compositions of the disclosure will be administered in a therapeutically effective amount by the desired mode of administration. Suitable dosage ranges depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compositions of the disclosure for a given disease.

In certain embodiments the pharmaceutical composition is in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10, 25, 50 or 100 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 50 to 500, 75 to 500, or 200 mg to about 600 mg of the active compounds and optionally for example from about 0.1 mg to about 2000 mg, from about 10, 25, 50 or 100 mg to about 1000 mg, from about 50 to 500, 75 to 500, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of an additional active agent in a unit dosage form. Examples are dosage forms with at least 0.1, 1, 5, 10, 25, 50, 100, 200, 250, 300, 400, 500, 600, 700, 750 or 800 mg of active compound, or its salt.

The therapeutically effective dosage of any active compound described herein will be determined by the health care practitioner depending on the condition, size and age of the patient as well as the route of delivery. In one non-limited

embodiment, a dosage from about 0.1 to about 200 mg/kg, from about 0.01 mg/kg to about 250 mg/kg body weight, more preferably about 0.1 mg/kg to up to about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20 or 30 mg/kg, in at least one dose. In some embodiments, the dosage may be the amount of compound needed to provide a serum concentration of the active compound of up to about 10 nM, 50 nM, 100 nM, 200 nM, 300 nM, 400 nM, 500 nM, 600 nM, 700 nM, 800 nM, 900 nM, 1 μM, 5 μM, 10 μM, 20 μM, 30 μM, or 40 μM.

The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a pill, an injection or infusion solution, a capsule, a tablet, a syrup, a transdermal patch, a subcutaneous patch, a dry powder, an inhalation formulation, in a medical device, suppository, buccal, or sublingual formulation, parenteral formulation, or an ophthalmic solution. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Edition (Easton, Pa.: Mack Publishing Company, 1990). For example, sterile saline and phosphate-buffered saline at physiological pH can be used. Preservatives, stabilizers, dyes and even flavoring agents can be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid can be added as preservatives. Id. at 1449. In addition, antioxidants and suspending agents can be used. Id. Carriers include excipients must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the disclosed compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound, as decribed in more detail herein.

Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidents, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin; talc, and vegetable oils. Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the disclosed compounds of the present invention.

Additionally, auxiliary substances, such as wetting or emulsifying agents, biological buffering substances, surfactants, and the like, can be present in such vehicles. A biological buffer can be any solution which is pharmacologically acceptable and which provides the formulation with the desired pH, i.e., a pH in the physiologically acceptable range. Examples of buffer solutions include saline, phosphate buffered saline, Tris buffered saline, Hank's buffered saline, and the like.

Depending on the intended mode of administration, the pharmaceutical compositions can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, can include other pharmaceutical agents, adjuvants, diluents, buffers, and the like.

Thus, the compositions of the disclosure can be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal or parenteral (including intramuscular, intra-arterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is intravenous or oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, and the like, an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and the like. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, referenced above.

In yet another embodiment is the use of permeation enhancer excipients including polymers such as: polycations (chitosan and its quaternary ammonium derivatives, poly-L-arginine, aminated gelatin); polyanions (N-carboxymethyl chitosan, poly-acrylic acid); and, thiolated polymers (carboxymethyl cellulose-cysteine, polycarbophil-cysteine, chitosan-thiobutylamidine, chitosan-thioglycolic acid, chitosan-glutathione conjugates).

For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule or can be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use can include one or more commonly used carriers such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. Typically, the compositions of the disclosure can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

When liquid suspensions are used, the active agent can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like and with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents can be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents, and the like.

Parenteral formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solubilization or suspension in liquid prior to injection, or as emulsions. Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable carriers, dispersing or wetting agents and suspending agents. The sterile injectable formulation can also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media. In addition, parenteral administration can involve the use of a slow release or sustained release system such that a constant level of dosage is maintained.

Parenteral administration includes intraarticular, intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, and include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Administration via certain parenteral routes can involve introducing the formulations of the disclosure into the body of a patient through a needle or a catheter, propelled by a sterile syringe or some other mechanical device such as an continuous infusion system. A formulation provided by the disclosure can be administered using a syringe, injector, pump, or any other device recognized in the art for parenteral administration.

Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable carriers, dispersing or wetting agents and suspending agents. The sterile injectable formulation can also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media. In addition, parenteral administration can involve the use of a slow release or sustained release system such that a constant level of dosage is maintained.

Preparations according to the disclosure for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms can also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They can be sterilized by, for example, filtration through a bacteria retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured using sterile water, or some other sterile injectable medium, immediately before use.

Sterile injectable solutions are prepared by incorporating one or more of the compounds of the disclosure in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Thus, for example, a parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Formulations suitable for rectal administration are typically presented as unit dose suppositories. These may be prepared by admixing the active disclosed compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (see, for example, *Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. In one embodiment, microneedle patches or devices are provided for delivery of drugs across or into biological tissue, particularly the skin. The microneedle patches or devices permit drug delivery at clinically relevant rates across or into skin or other tissue barriers, with minimal or no damage, pain, or irritation to the tissue.

Formulations suitable for administration to the lungs can be delivered by a wide range of passive breath driven and active power driven single/-multiple dose dry powder inhalers (DPI). The devices most commonly used for respiratory delivery include nebulizers, metered-dose inhalers, and dry powder inhalers. Several types of nebulizers are available, including jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers. Selection of a suitable lung delivery device depends on parameters, such as nature of the drug and its formulation, the site of action, and pathophysiology of the lung.

Additional non-limiting examples of drug delivery devices and methods include, for example, US20090203709 titled "Pharmaceutical Dosage Form For Oral Administration Of Tyrosine Kinase Inhibitor" (Abbott Laboratories); US20050009910 titled "Delivery of an active drug to the posterior part of the eye via subconjunctival or periocular delivery of a prodrug", US 20130071349 titled "Biodegradable polymers for lowering intraocular pressure", U.S. Pat. No. 8,481,069 titled "Tyrosine kinase microspheres", U.S. Pat. No. 8,465,778 titled "Method of making tyrosine kinase

microspheres", U.S. Pat. No. 8,409,607 titled "Sustained release intraocular implants containing tyrosine kinase inhibitors and related methods", U.S. Pat. No. 8,512,738 and US 2014/0031408 titled "Biodegradable intravitreal tyrosine kinase implants", US 2014/0294986 titled "Microsphere Drug Delivery System for Sustained Intraocular Release", U.S. Pat. No. 8,911,768 titled "Methods For Treating Retinopathy With Extended Therapeutic Effect" (Allergan, Inc.); U.S. Pat. No. 6,495,164 titled "Preparation of injectable suspensions having improved injectability" (Alkermes Controlled Therapeutics, Inc.); WO 2014/047439 titled "Biodegradable Microcapsules Containing Filling Material" (Akina, Inc.); WO 2010/132664 titled "Compositions And Methods For Drug Delivery" (Baxter International Inc. Baxter Healthcare SA); US20120052041 titled "Polymeric nanoparticles with enhanced drug loading and methods of use thereof" (The Brigham and Women's Hospital, Inc.); US20140178475, US20140248358, and US20140249158 titled "Therapeutic Nanoparticles Comprising a Therapeutic Agent and Methods of Making and Using Same" (BIND Therapeutics, Inc.); U.S. Pat. No. 5,869,103 titled "Polymer microparticles for drug delivery" (Danbiosyst UK Ltd.); U.S. Pat. No. 8,628,801 titled "Pegylated Nanoparticles" (Universidad de Navarra); US2014/0107025 titled "Ocular drug delivery system" (Jade Therapeutics, LLC); U.S. Pat. No. 6,287,588 titled "Agent delivering system comprised of microparticle and biodegradable gel with an improved releasing profile and methods of use thereof", U.S. Pat. No. 6,589,549 titled "Bioactive agent delivering system comprised of microparticles within a biodegradable to improve release profiles" (Macromed, Inc.); U.S. Pat. Nos. 6,007,845 and 5,578,325 titled "Nanoparticles and microparticles of non-linear hydrophilic hydrophobic multiblock copolymers" (Massachusetts Institute of Technology); US20040234611, US20080305172, US20120269894, and US20130122064 titled "Ophthalmic depot formulations for periocular or subconjunctival administration (Novartis Ag); U.S. Pat. No. 6,413,539 titled "Block polymer" (Poly-Med, Inc.); US 20070071756 titled "Delivery of an agent to ameliorate inflammation" (Peyman); US 20080166411 titled "Injectable Depot Formulations And Methods For Providing Sustained Release Of Poorly Soluble Drugs Comprising Nanoparticles" (Pfizer, Inc.); U.S. Pat. No. 6,706,289 titled "Methods and compositions for enhanced delivery of bioactive molecules" (PR Pharmaceuticals, Inc.); and U.S. Pat. No. 8,663,674 titled "Microparticle containing matrices for drug delivery" (Surmodics).

VI. General Synthesis

The compounds described herein can be prepared by methods known by those skilled in the art. In one non-limiting example the disclosed compounds can be made by the following schemes.

Compounds of the present invention with stereocenters may be drawn without stereochemistry for convenience. One skilled in the art will recognize that pure enantiomers and diastereomers can be prepared by methods known in the art. Examples of methods to obtain optically active materials include at least the following.

i) Physical separation of crystals—a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;

ii) Simultaneous crystallization—a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) Enzymatic resolutions—a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme; iv) Enzymatic asymmetric synthesis—a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) Chemical asymmetric synthesis—a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) Diastereomer separations—a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) First- and second-order asymmetric transformations-a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) Kinetic resolutions—this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) Enantiospecific synthesis from non-racemic precursors-a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) Chiral liquid chromatography-a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase (including via chiral HPLC). The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

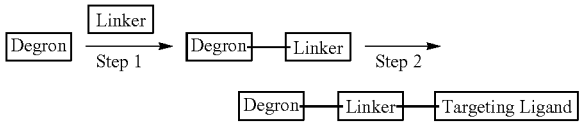
xi) Chiral gas chromatography-a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

xii) Extraction with chiral solvents-a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

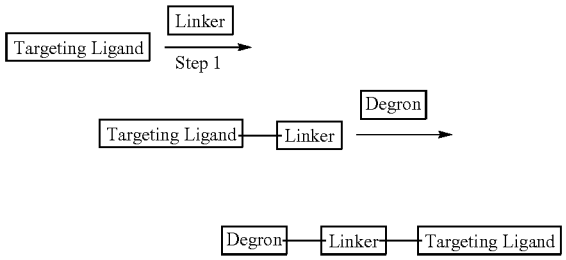
xiii) Transport across chiral membranes-a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through.

xiv) Chiral chromatography, including simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

Scheme 1

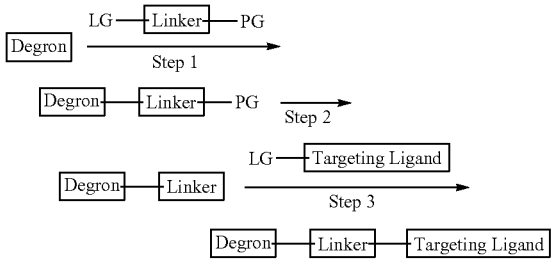


Scheme 2



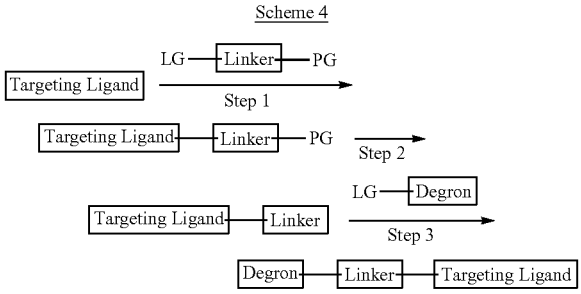
As shown in Scheme 1 compounds for use in the present invention can be prepared by chemically combining a Degron and a Linker followed by subsequent addition of a Targeting Ligand. Similarly, in Scheme 2 compounds for use in the present invention are prepared by chemically combing a Targeting Ligand and Linker first, followed by subsequent addition of a Degron. As illustrated in the above and following schemes, compounds for use in the present invention can readily be synthesized by one skilled in the art in a variety of methods and chemical reactions.

Scheme 3



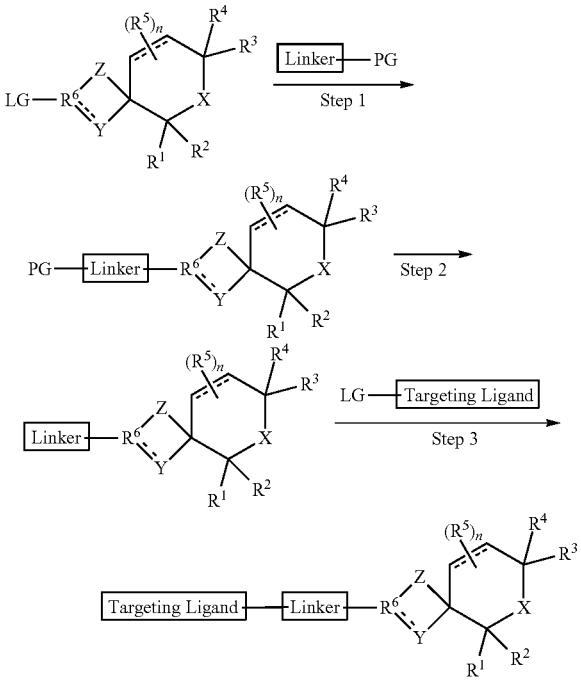
Scheme 3: In Step 1, a nucleophilic Degron displaces a leaving group on the Linker to make a Degron Linker fragment. In Step 2, the protecting group is removed by methods known in the art to free a nucleophilic site on the Linker. In Step 3, the nucleophilic Degron Linker fragment displaces a leaving group on the Targeting Ligand to form a compound for use in the present invention. In an alternative embodiment Step 1 and/or Step 2 is accomplished by a coupling reaction instead of a nucleophilic attack.

Scheme 4

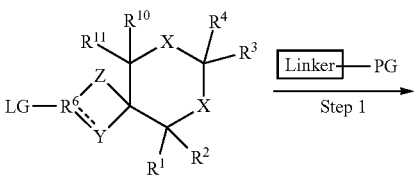


Scheme 4: In Step 1, a nucleophilic Targeting Ligand displaces a leaving group on the Linker to make a Targeting Ligand Linker fragment. In Step 2, the protecting group is removed by methods known in the art to free a nucleophilic site on the Linker. In Step 3, the nucleophilic Targeting Ligand Linker fragment displaces a leaving group on the Degron to form a compound for use in the present invention. In an alternative embodiment Step 1 and/or Step 2 is accomplished by a coupling reaction instead of a nucleophilic attack.

Scheme 5



Scheme 6



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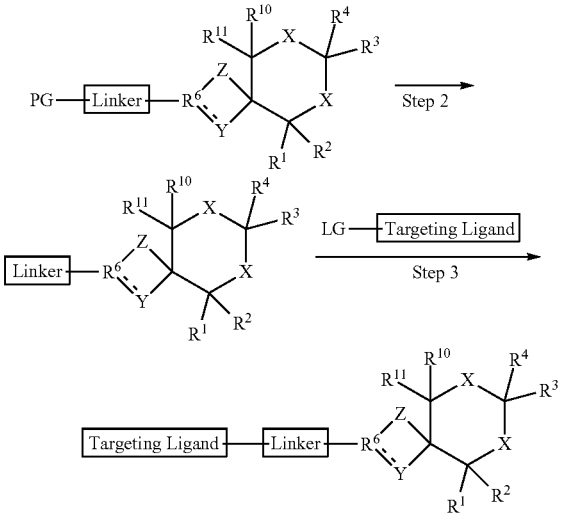
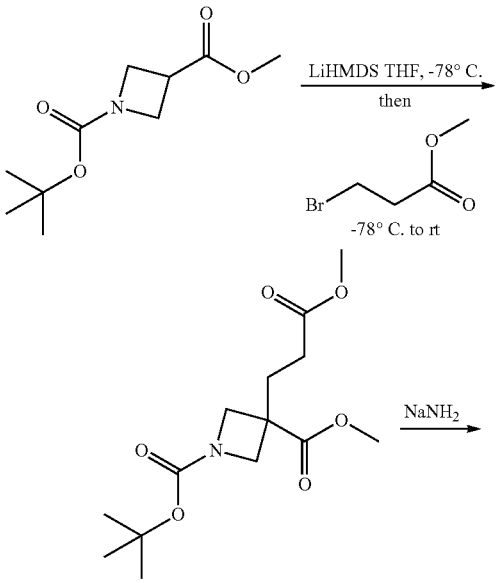


Scheme 5 and Scheme 6: In Step 1, a nucleophilic Linker displaces a leaving group on the Degron to make a Degron Linker fragment. In Step 2, the protecting group is removed by methods known in the art to free a nucleophilic site on the Linker. In Step 3, the nucleophilic Degron Linker fragment displaces a leaving group on the Targeting Ligand to form a compound of Formula I or Formula II. In an alternative embodiment Step 1 and/or Step 2 is accomplished by a coupling reaction instead of a nucleophilic attack.

VII. Synthesis of Representative Compounds

Exemplary processes to prepare the compounds of the present invention are provided below. Given this disclosure, one of ordinarily skill in the art can prepare the scope of compounds of Formula I, II, III and IV.

Representative Example 1:
2,6-Diazaspiro[3.5]nonane-5,7-dione



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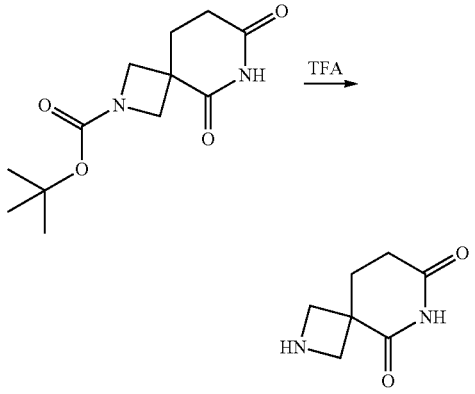
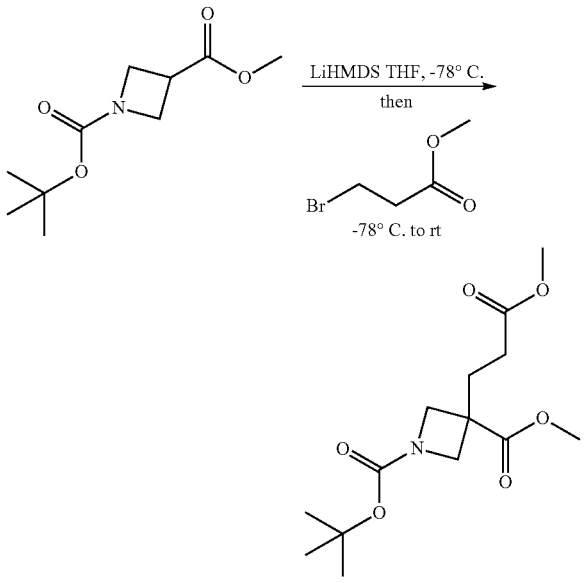
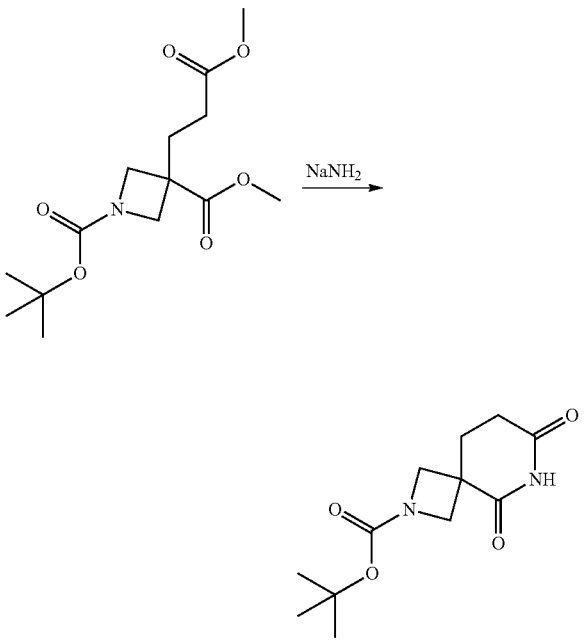


1-(tert-Butyl) 3-methyl 3-(3-methoxy-3-oxopropyl) azetidine-1,3-dicarboxylate



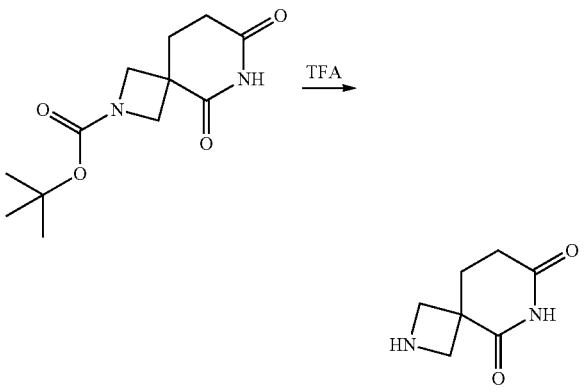
1-(Tert-butyl) 3-methyl azetidine-1,3-dicarboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of lithium hexamethyldisilazide (1.0 M in tetrahydrofuran) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)azetidine-1,3-dicarboxylate (Synlett, 2015, 26, 1815-1818.).

tert-Butyl 5,7-dioxo-2,6-diazaspiro[3.5]nonane-2-carboxylate



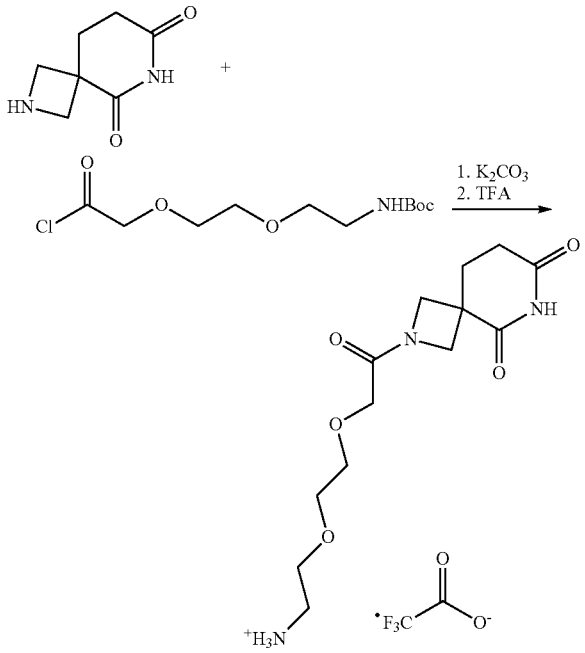
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)azetidine-1,3-dicarboxylate in tetrahydrofuran at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide tert-butyl 5,7-dioxo-2,6-diazaspiro[3.5]nonane-2-carboxylate (Synthesis, 1985, (4), 402-403.).

2,6-Diazaspiro[3.5]nonane-5,7-dione



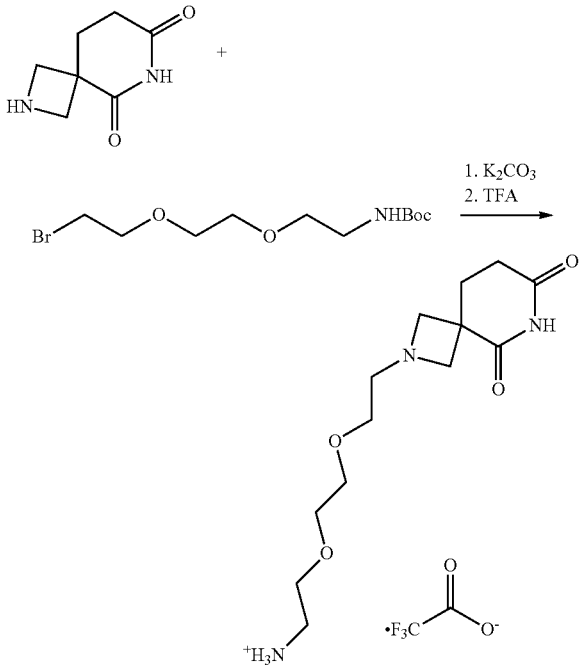
To a solution of tert-butyl 5,7-dioxo-2,6-diazaspiro[3.5]nonane-2-carboxylate in dichloromethane was added a solution of 30% trifluoroacetic acid in dichloromethane at 0° C. The resulting solution stirred at room temperature for 2 hours. The reaction was then quenched with aqueous saturated sodium bicarbonate solution and diluted with dichloromethane. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under vacuum. The crude residue was purified on silica using a gradient of 1:1 methanol:ammonia in dichloromethane to yield 2,6-diazaspiro[3.5]nonane-5,7-dione.

2-(2-(2-(5,7-Dioxo-2,6-diazaspiro [3.5] nonan-2-yl)-2-oxoethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate



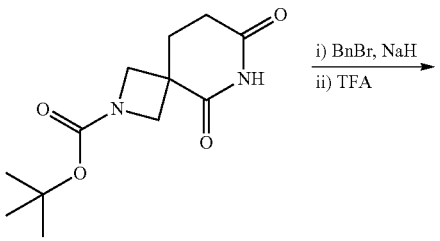
2,6-Diazaspiro[3.5]nonane-5,7-dione is dissolved in dry dichloromethane. Powdered potassium carbonate (3 equiv.) is added followed by tert-butyl (2-(2-(2-chloro-2-oxoethoxy)ethoxy)ethyl)carbamate (derived from 2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-oic acid, 1 equiv.). The mixture is allowed to stir for 2 hours and then quenched by adding aqueous saturated sodium bicarbonate solution and diluting with dichloromethane. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate. The crude material is then dissolved in dichloromethane and a 30% solution of trifluoroacetic acid in dichloromethane is added. The mixture is allowed to stir at room temperature until the reaction is judged complete by TLC or LCMS analysis. The mixture is then concentrated under reduced pressure to give the desired trifluoroacetate salt.

2-(2-(2-(5,7-Dioxo-2,6-diazaspiro [3.5] nonan-2-yl) ethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate



2,6-Diazaspiro[3.5]nonane-5,7-dione is dissolved in dry N,N-dimethylformamide. Powdered potassium carbonate (3 equiv.) is added followed by tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate. The reaction mixture is heated to 40° C. and allowed to stir for 12 hours. The reaction mixture is then cooled to room temperature and partitioned between ethyl acetate and brine. The organic layer is washed again with brine, dried over sodium sulfate and then concentrated under reduced pressure (U.S. Pat. Appl. Publ., 20080269234). The crude material is then dissolved in dichloromethane and a 30% solution of trifluoroacetic acid in dichloromethane is added. The mixture is allowed to stir at room temperature until the reaction is judged complete by TLC or LCMS analysis. The mixture is then concentrated under reduced pressure to give the desired trifluoroacetate salt.

6-Benzyl-2,6-diazaspiro[3.5]nonane-5,7-dione



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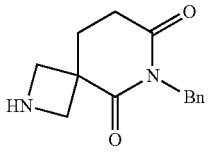
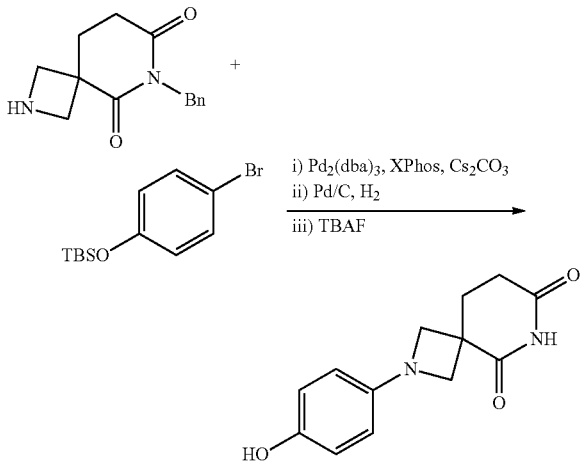


t-Butyl 5,7-dioxo-2,6-diazaspiro[3.5]nonane-2-carboxylate is dissolved in dry tetrahydrofuran and cooled to 0° C. Sodium hydride (1.1 equiv., 60% dispersion in mineral oil) is added and the mixture is allowed to stir for 30 minutes. Benzyl bromide (1.5 equiv.) is then added dropwise. The reaction mixture is allowed to warm slowly to room temperature and stir until the reaction is judged complete by TLC or LCMS analysis. It is then quenched with a saturated aqueous solution of ammonium chloride and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is then dissolved in dichloromethane and a 30% solution of trifluoroacetic acid in dichloromethane is added. The mixture is allowed to stir at room temperature until the reaction is judged complete by TLC or LCMS analysis and then quenched with a saturated aqueous solution of sodium bicarbonate. The mixture is diluted with dichloromethane and the organic layer is separated. The aqueous layer is extracted with dichloromethane (3×) and the combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting amine is purified on silica using a gradient of 1:1 methanol:ammonia in dichloromethane.

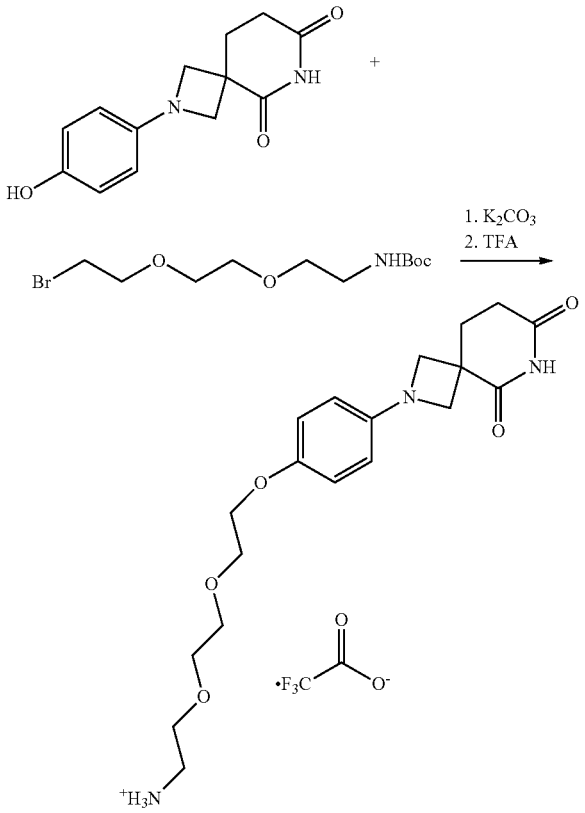
2-(4-Hydroxyphenyl)-2,6-diazaspiro [3.5] nonane-5,7-dione



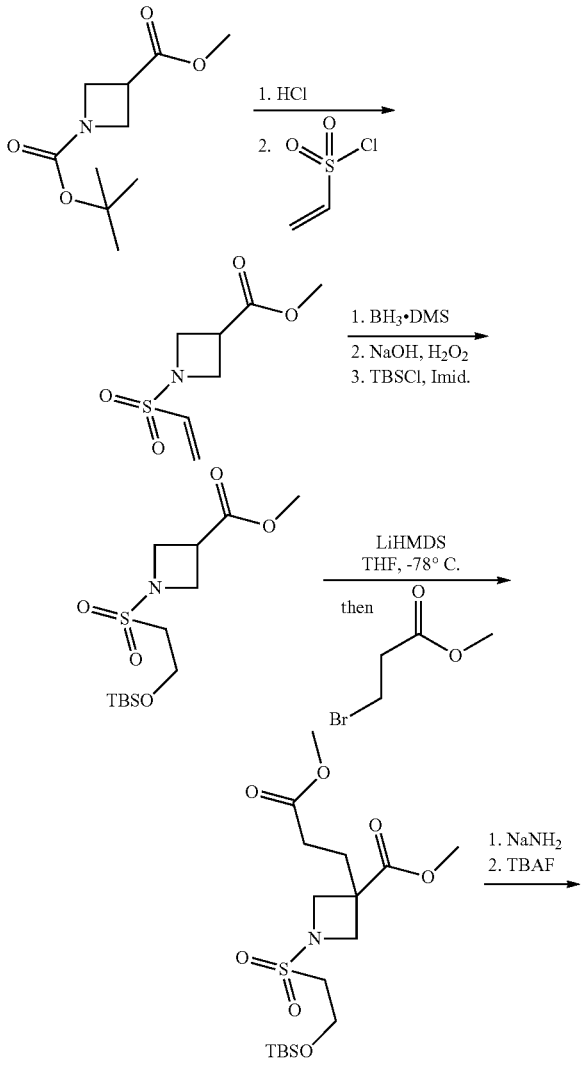
To a stirred solution of 6-benzyl-2,6-diazaspiro[3.5] nonane-5,7-dione (1 equiv.), (4-bromophenoxy)(tert-butyl) dimethylsilane (1 equiv.), cesium carbonate (4 equiv.), and X-Phos (0.5 equiv.) in dry dioxane is added $Pd_2(dba)_3$ (0.1 equiv.) under nitrogen atmosphere. The reaction mixture is degassed with nitrogen for 15 minutes and then heated to 95° C. When the reaction is judged to be complete based on TLC or LCMS analysis, it is cooled to room temperature and concentrated under reduced pressure. The crude material is

then purified on silica to give the desired coupling product (PCT Int. Appl. 2012130780). The benzyl protected imide is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness. The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 2-(4-hydroxyphenyl)-2,6-diazaspiro[3.5] nonane-5,7-dione.

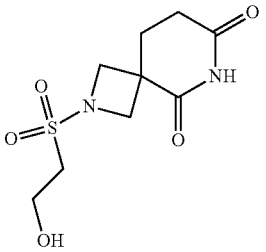
2-(2-(2-(4-(5,7-Dioxo-2,6-diazaspiro [3.5]nonan-2-yl)phenoxy)ethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate



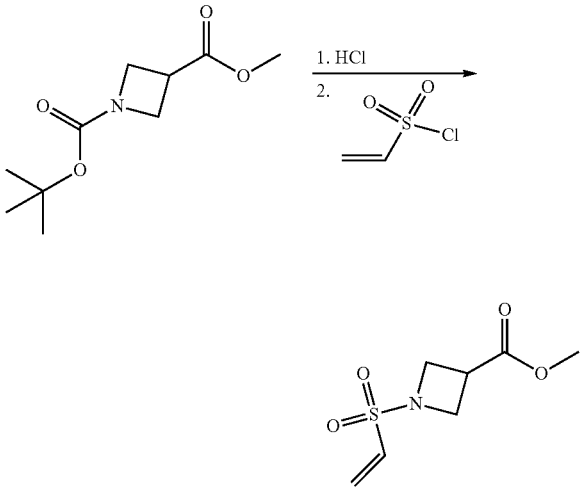
2-(4-Hydroxyphenyl)-2,6-diazaspiro[3.5]nonane-5,7-dione is dissolved in dry N,N-dimethylformamide. Powdered potassium carbonate (3 equiv.) is added followed by tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate. The reaction mixture is heated to 40° C. and allowed to stir for 12 hours. The reaction mixture is then cooled to room temperature and partitioned between ethyl acetate and brine. The organic layer is washed again with brine, dried over sodium sulfate and then concentrated under reduced pressure (U.S. Pat. Appl. Publ., 20080269234). The crude material is then dissolved in dichloromethane and a 30% solution of trifluoroacetic acid in dichloromethane is added. The mixture is allowed to stir at room temperature until the reaction is judged complete by TLC or LCMS analysis. The mixture is then concentrated under reduced pressure to give the desired trifluoroacetate salt.



Representative Example 2: 2-((2-Hydroxyethyl) sulfonyl)-2,6-diazaspiro[3.5]nonane-5,7-dione

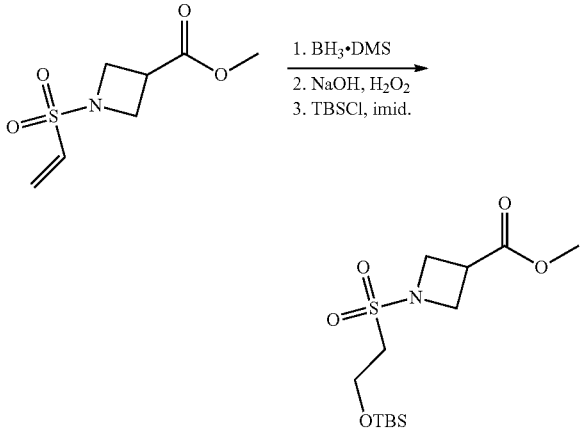


Methyl 1-(vinylsulfonyl)azetidine-3-carboxylate



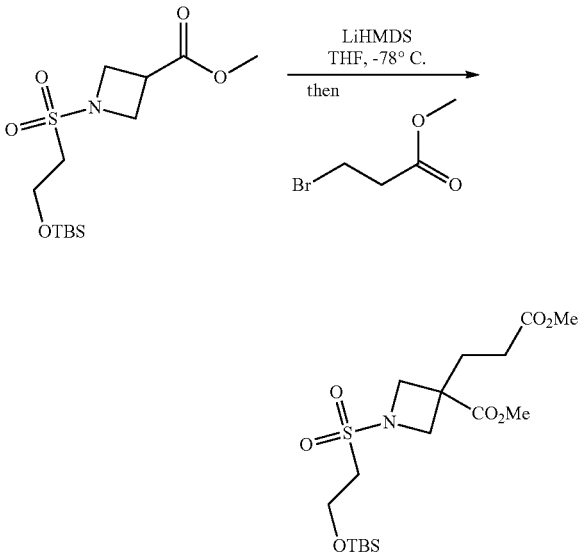
The Boc-protected azetidine is dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure. The azetidine (1 equiv.) is then dissolved in DCM and cooled to −40° C. Triethylamine (1.5 equiv.) is added followed by DMAP (0.1 equiv.). A solution of vinylsulfonyl chloride (1.2 equiv.) in DCM was added slowly, dropwise. The mixture is allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The reaction is then allowed to warm to room temperature and filtered through silica gel. The filtrate was concentrated under reduced pressure and the crude material was purified on silica.

Methyl 1-((2-((tert-butyldimethylsilyl)oxy)ethyl) sulfonyl)azetidine-3-carboxylate



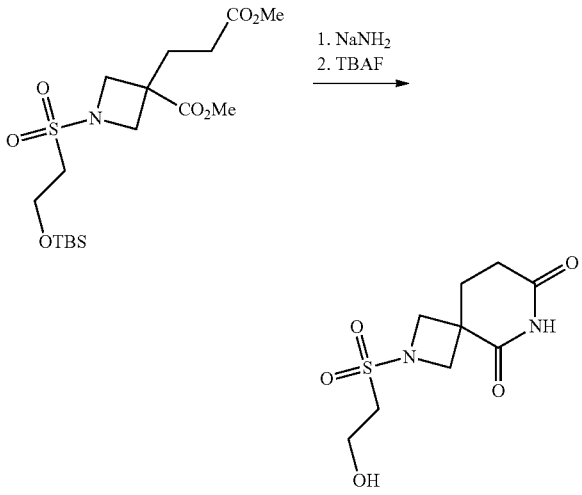
The vinyl sulfone (1 equiv.) is dissolved in THF. Borane-dimethylsulfide in THF (2.0M, 1 equiv.) is added. The resulting solution is stirred at room temperature for 30 minutes. Hydrogen peroxide solution (30% w/v, 1 equiv.) and sodium hydroxide (2 N, 1 equiv.) is added to the reaction mixture which is allowed to stir for 24 hours. The mixture is then partitioned between ethyl acetate and water. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is then dissolved in DCM. Imidazole (2 equiv.) is added followed by TBSCl (1 equiv.). The mixture is allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then diluted with water and DCM. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is then purified on silica to afford methyl 1-((2-((tert-butyldimethylsilyl)oxy) ethyl)sulfonyl)azetidine-3-carboxylate.

Methyl-1-((2-((tert-butyldimethylsilyl)oxy)ethyl) sulfonyl)-3-(3-methoxy-3-oxopropyl)azetidine-3-carboxylate



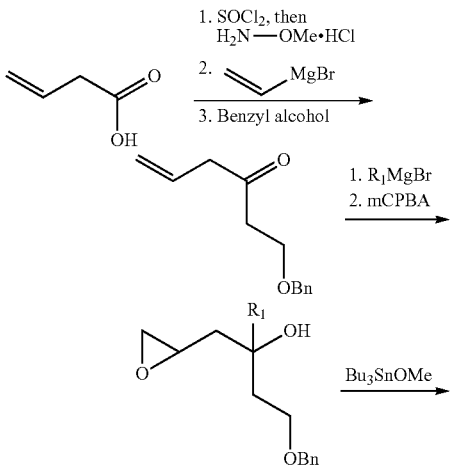
1-(Tert-butyl) 3-methyl azetidine-1,3-dicarboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of lithium hexamethyldisilazide (1.0 M in tetrahydrofuran) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 1-((2-((tert-butyldimethylsilyl)oxy)ethyl)sulfonyl)-3-(3-methoxy-3-oxopropyl)azetidine-3-carboxylate (Synlett, 2015, 26, 1815-1818.).

2-((2-Hydroxyethyl)sulfonyl)-2,6-diazaspiro [3.5] nonane-5,7-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)azetidine-1,3-dicarboxylate in tetrahydrofuran at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated under reduced pressure (Synthesis, 1985, (4), 402-403.). The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 2-((2-hydroxyethyl)sulfonyl)-2,6-diazaspiro[3.5]nonane-5,7-dione.

General Scheme



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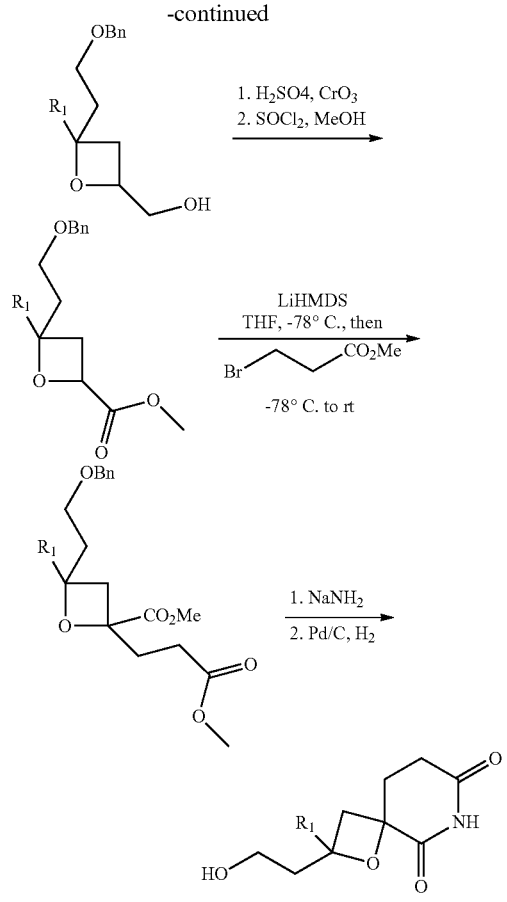
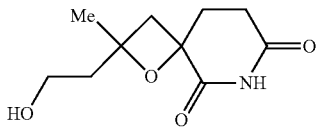
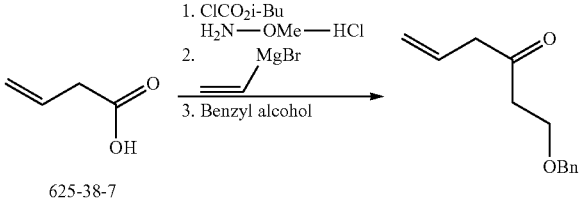


Representative Example 3: 2-(2-Hydroxyethyl)-2-methyl-1-oxa-6-azaspiro[3.5]nonane-5,7-dione



1-(Benzyloxy)hex-5-en-3-one

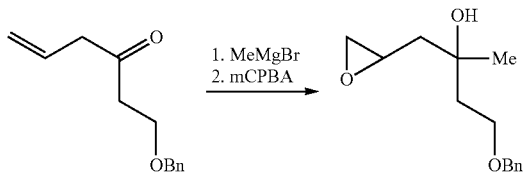


625-38-7

To a solution of 4-butenoic acid (1 equiv.) in dichloromethane at 0° C. is added trimethylamine (2 equiv.), isobutyl chloroformate (1.1 equiv.) and N,O-dimethylhydroxylamine (1.05 equiv.), followed by trimethylamine (2 equiv.). The reaction is stirred overnight at room tempera-

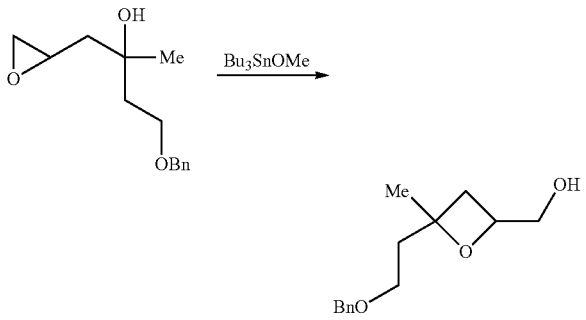
ture. It is then treated with a saturated aqueous solution of sodium bicarbonate. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is purified on silica (Goncalves-Martin, M.; et al., Synlett, 2009, 17, 2801-2802). The Weinreb amide is then dissolved in dry tetrahydrofuran and cooled to 0° C. Vinyl Grignard reagent (0.7 M in THF, 1.2 equiv.) is then added dropwise. After 1 hour the reaction is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting material was purified over silica (Yu, L.-F.; et al. J. Org. Chem., 2011, 76, 1448-1451). The resulting enone is dissolved in dichloromethane. Benzyl alcohol (2 equiv.) is added followed by concentrated sulfuric acid (0.05 equiv.). The reaction is stirred at room temperature overnight and then quenched with saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting crude material was purified on silica (PCT Int. Appl., 2006085118).

4-(Benzyloxy)-2-methyl-1-(oxiran-2-yl)butan-2-ol



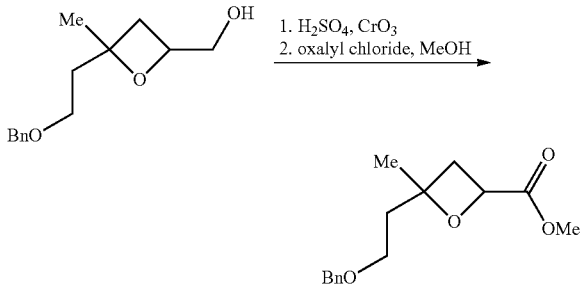
1-(Benzyloxy)hex-5-en-3-one (1 equiv.) is dissolved in dry diethyl ether and cooled to 0° C. Methyl magnesium bromide (1.0 M in THF, 1 equiv.) is added to the solution which is allowed to warm gradually to room temperature. When the reaction is judged complete based on TLC or LCMS analysis, it is quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The tertiary alcohol is then dissolved in DCM and mCPBA (1.2 equiv.) was added portionwise across 30 minutes. The reaction is allowed to stir until it is judged complete by TLC or LCMS analysis. The reaction is then quenched with 1.0 M sodium thiosulfate solution. The reaction is diluted with DCM and the organic layer is separated. The organic layer is then washed with saturated sodium bicarbonate solution and then brine solution before drying over sodium sulfate and concentrating under reduced pressure. The resulting material was purified on silica to give the desired terminal epoxide.

(4-(2-(Benzyloxy)ethyl)-4-methyloxetan-2-yl)methanol



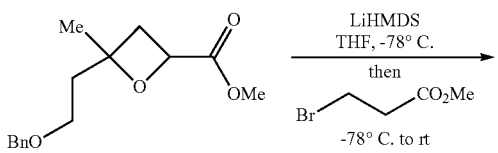
Procedure provided in Bats, J.; Moulines, J.; Pommier, J. C. Tetrahedron Lett. 1976, 26, 2249-2250, and Griffiths, G.; Stirling, C. J. M. Heterocycles, 1989, 28, 89-92.

Methyl 4-(2-(benzyloxy)ethyl)-4-methyloxetane-2-carboxylate



(4-(2-(Benzyloxy)ethyl)-4-methyloxetan-2-yl)methanol is dissolved in acetone. Jones' reagent is added slowly dropwise until the reaction was judged complete by TLC or LCMS analysis. Isopropanol is then added to quench the remaining chromium. The solids formed are filtered off and the filtrate is evaporated to dryness. The crude material is taken up in ethyl acetate, washed with water and then brine, dried over sodium sulfate and concentrated under reduced pressure to afford 4-(2-(benzyloxy)ethyl)-4-methyloxetane-2-carboxylic acid. The carboxylic acid is then dissolved in dichloromethane. Oxalyl chloride (2 equiv.) is added followed by DMF (1 drop). The reaction is allowed to stir for 2 hours and is then quenched with methanol. The reaction mixture is then concentrated yielding the desired methyl ester.

Methyl 4-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-4-methyloxetane-2-carboxylate



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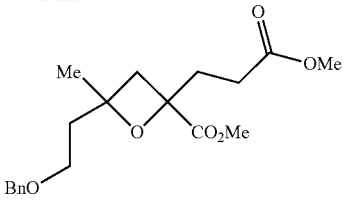
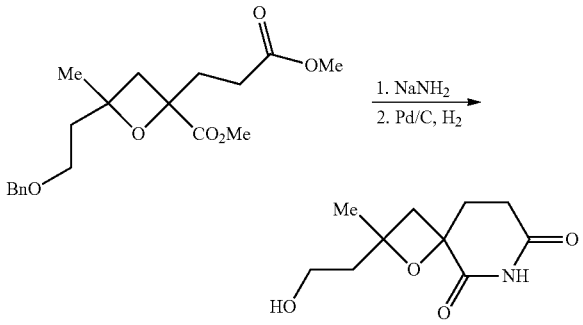


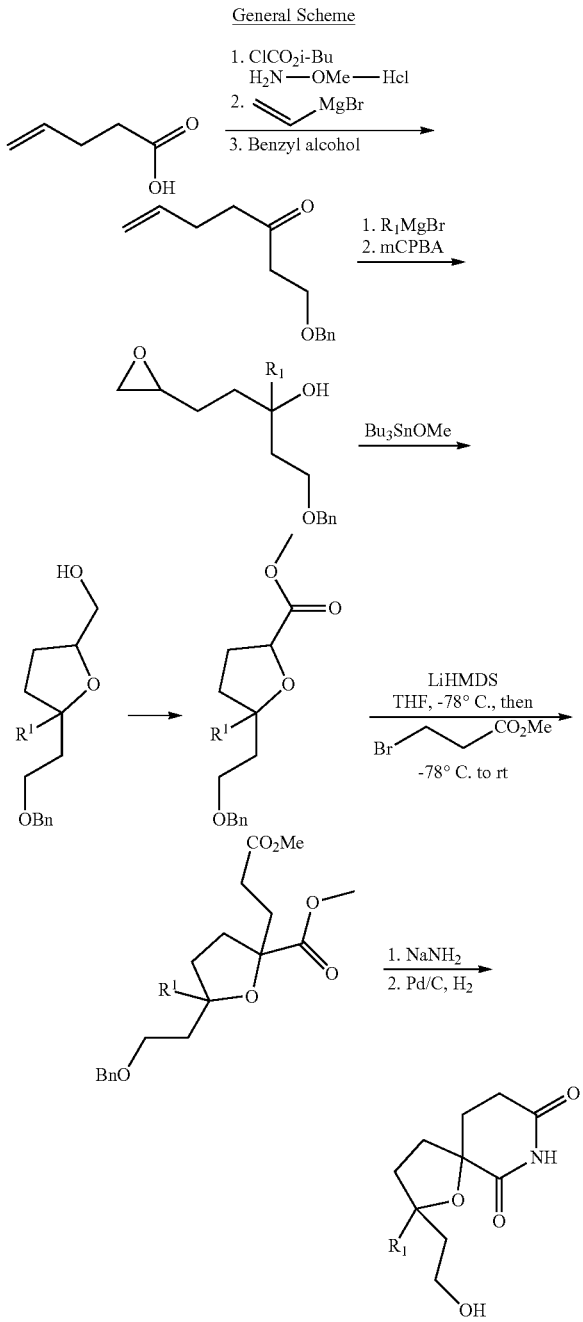
Methyl 4-(2-(benzyloxy)ethyl)-4-methyloxetane-2-carboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. This is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 4-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-4-methyloxetane-2-carboxylate.

2-(2-Hydroxyethyl)-2-methyl-1-oxa-6-azaspiro[3.5]nonane-5,7-dione

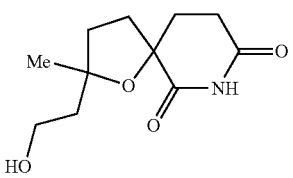


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 4-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-4-methyloxetane-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 2-(2-hydroxyethyl)-2-methyl-1-oxa-6-azaspiro[3.5]nonane-5,7-dione.

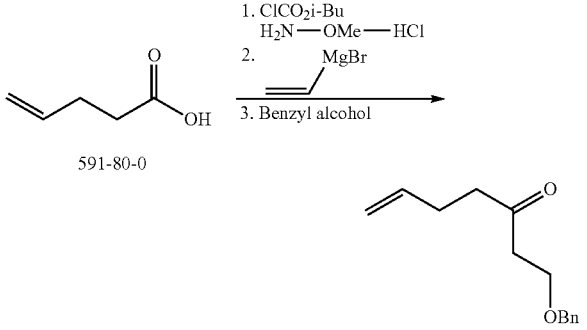
General Scheme



Representative Example 4: 2-(2-Hydroxyethyl)-2-methyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione

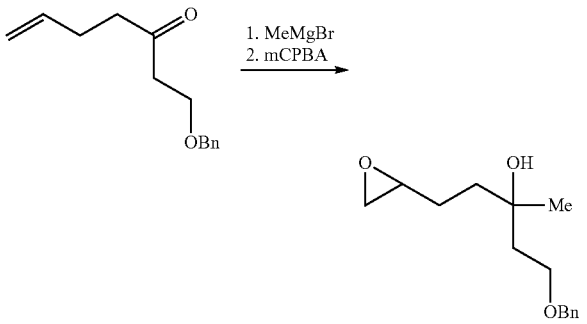


1-(Benzyloxy)hept-6-en-3-one



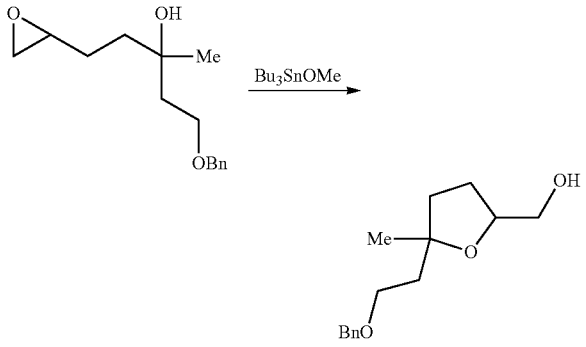
To a solution of 4-penenoic acid (1 equiv.) in dichloromethane at 0° C. is added trimethylamine (2 equiv.), isobutyl chloroformate (1.1 equiv.) and N,O-dimethylhydroxylamine (1.05 equiv.), followed by trimethylamine (2 equiv.). The reaction is stirred overnight at room temperature. It is then treated with a saturated aqueous solution of sodium bicarbonate. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is purified on silica (Goncalves-Martin, M.; et al., Synlett, 2009, 17, 2801-2802.). The Weinreb amide is then dissolved in dry tetrahydrofuran and cooled to 0° C. Vinyl Grignard reagent (0.7 M in THF, 1.2 equiv.) is then added dropwise. After 1 hour the reaction is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting material was purified over silica (Yu, L.-F.; et al. J. Org. Chem., 2011, 76, 1448-1451.). The resulting enone is dissolved in dichloromethane. Benzyl alcohol (2 equiv.) is added followed by concentrated sulfuric acid (0.05 equiv.). The reaction is stirred at room temperature overnight and then quenched with saturated sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting crude material was purified on silica (PCT Int. Appl., 2006085118).

1-(Benzyloxy)-3-methyl-5-(oxiran-2-yl)pentan-3-ol



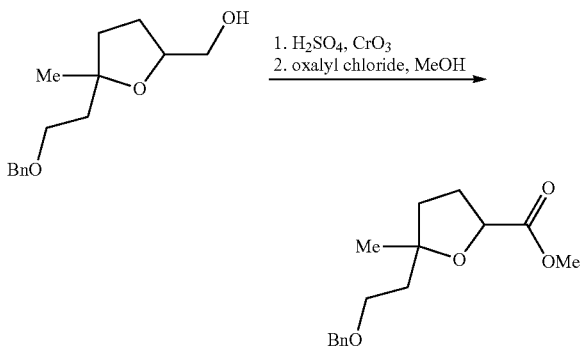
1-(Benzyloxy)hept-6-en-3-one (1 equiv.) is dissolved in dry diethyl ether and cooled to 0° C. Methyl magnesium bromide (1.0 M in THF, 1 equiv.) is added to the solution which is allowed to warm gradually to room temperature. When the reaction is judged complete based on TLC or LCMS analysis, it is quenched with saturated ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The tertiary alcohol is then dissolved in DCM and mCPBA (1.2 equiv.) was added portionwise across 30 minutes. The reaction is allowed to stir until it is judged complete by TLC or LCMS analysis. The reaction is then quenched with 1.0 M sodium thiosulfate solution. The reaction is diluted with DCM and the organic layer is separated. The organic layer is then washed with saturated sodium bicarbonate solution and then brine solution before drying over sodium sulfate and concentrating under reduced pressure. The resulting material was purified on silica to give the desired terminal epoxide.

(5-(2-(Benzyloxy)ethyl)-5-methyltetrahydrofuran-2-yl)methanol



Procedure provided in Bats, J.; Moulines, J.; Pommier, J. C. Tetrahedron Lett. 1976, 26, 2249-2250, and Griffiths, G.; Stirling, C. J. M. Heterocycles, 1989, 28, 89-92.

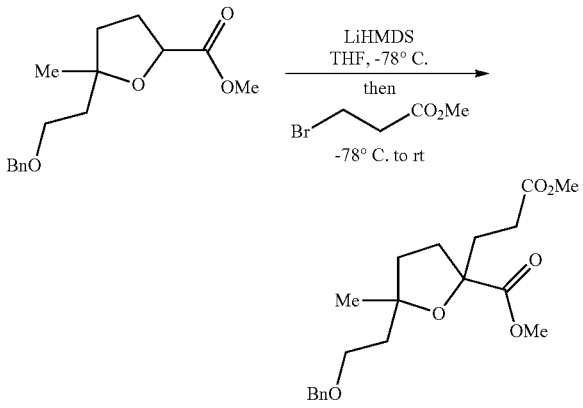
Methyl 5-(2-(benzyloxy)ethyl)-5-methyltetrahydrofuran-2-carboxylate



(5-(2-(Benzyloxy)ethyl)-5-methyltetrahydrofuran-2-yl) methanol is dissolved in acetone. Jones' reagent is added

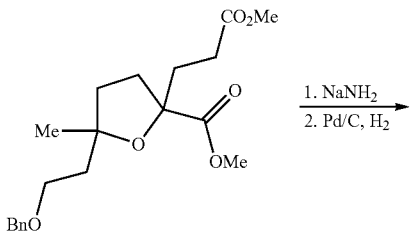
slowly dropwise until the reaction was judged complete by TLC or LCMS analysis. Isopropanol is then added to quench the remaining chromium. The solids formed are filtered off and the filtrate is evaporated to dryness. The crude material is taken up in ethyl acetate, washed with water and then brine, dried over sodium sulfate and concentrated under reduced pressure to afford 5-(2-(benzyloxy)ethyl)-5-methyltetrahydrofuran-2-carboxylic acid. The carboxylic acid is then dissolved in dichloromethane. Oxalyl chloride (2 equiv.) is added followed by DMF (1 drop). The reaction is allowed to stir for 2 hours and is then quenched with methanol. The reaction mixture is then concentrated yielding the desired methyl ester.

Methyl 5-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-5-methyltetrahydrofuran-2-carboxylate



Methyl 5-(2-(benzyloxy)ethyl)-5-methyltetrahydrofuran-2-carboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 5-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-5-methyltetrahydrofuran-2-carboxylate.

2-(2-Hydroxyethyl)-2-methyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione



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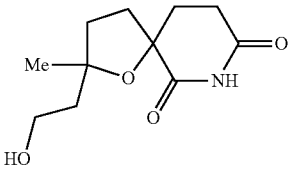
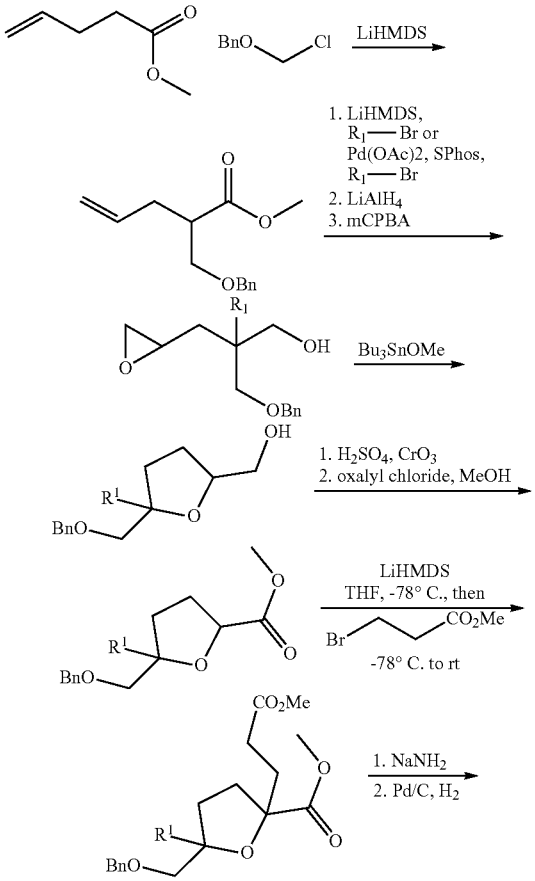


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 5-(2-(benzyloxy)ethyl)-2-(3-methoxy-3-oxopropyl)-5-methyltetrahydrofuran-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 2-(2-hydroxyethyl)-2-methyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione.

General Scheme



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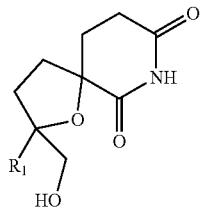
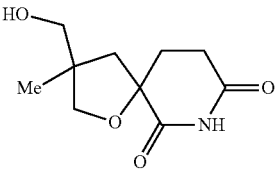
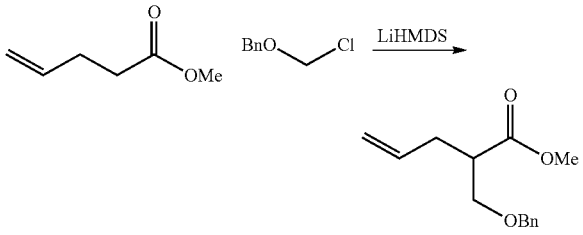


Representative Example 5: 3-(Hydroxymethyl)-3-methyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione

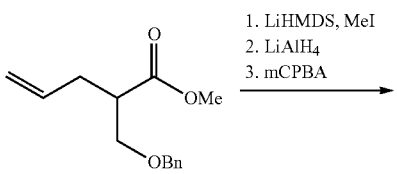


Methyl 2-((benzyloxy)methyl)pent-4-enoate



Methyl pent-4-enoate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. ((chloromethoxy)methyl)benzene (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 2-((benzyloxy)methyl)pent-4-enoate.

3-(Benzyloxy)-2-methyl-2-(oxiran-2-ylmethyl)propan-1-ol



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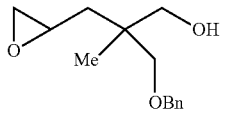
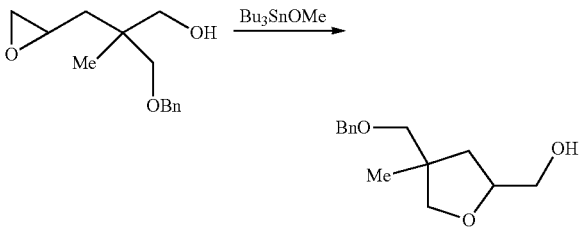


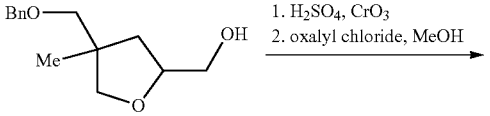
Methyl 2-((benzyloxy)methyl)pent-4-enoate. (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl iodide (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then taken up in diethyl ether and added, slowly, dropwise to a suspension of $LiAlH_4$ (1 equiv.) in dry diethyl ether at 0° C. The mixture is allowed to stir for 2 hours. Water (1 mL/g of $LiAlH_4$) was added slowly at 0° C. Aqueous sodium hydroxide solution (15% w/w, 1 mL/g of $LiAlH_4$) was added followed by another addition of water (3 mL/g of $LiAlH_4$). Magnesium sulfate was then added and the mixture was allowed to stir for 30 minutes. The salts were then filtered off and the filtrate was concentrated under reduced pressure. The tertiary alcohol is then dissolved in DCM and mCPBA (1.2 equiv.) was added portionwise across 30 minutes. The reaction is allowed to stir until it is judged complete by TLC or LCMS analysis. The reaction is then quenched with 1.0 M sodium thiosulfate solution. The reaction is diluted with DCM and the organic layer is separated. The organic layer is then washed with saturated sodium bicarbonate solution and then brine solution before drying over sodium sulfate and concentrating under reduced pressure. The resulting material was purified on silica to give the desired terminal epoxide.

(4-((Benzyloxy)methyl)-4-methyltetrahydrofuran-2-yl)methanol



Procedure provided in Bats, J, Moulines, J.; Pommier, J. C. Tetrahedron Lett. 1976, 26, 2249-2250, and Griffiths, G.; Stirling, C. J. M. Heterocycles, 1989, 28, 89-92.

Methyl 4-((benzyloxy)methyl)-4-methyltetrahydrofuran-2-carboxylate



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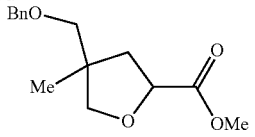
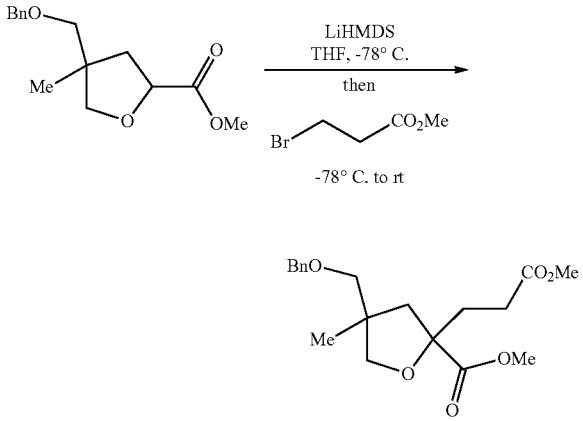


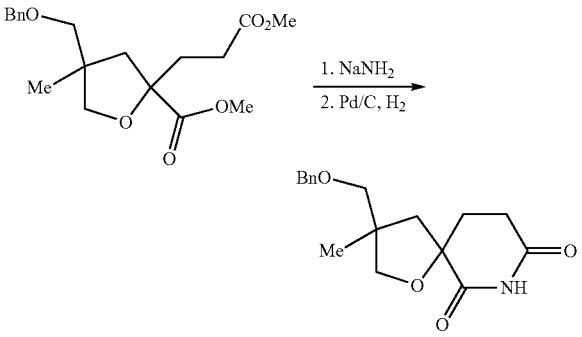
(4-((Benzyloxy)methyl)-4-methyltetrahydrofuran-2-yl) methanol is dissolved in acetone. Jones' reagent is added slowly dropwise until the reaction was judged complete by TLC or LCMS analysis. Isopropanol is then added to quench the remaining chromium. The solids formed are filtered off and the filtrate is evaporated to dryness. The crude material is taken up in ethyl acetate, washed with water and then brine, dried over sodium sulfate and concentrated under reduced pressure to afford 4-((benzyloxy)methyl)-4-methyltetrahydrofuran-2-carboxylic acid. The carboxylic acid is then dissolved in dichloromethane. Oxalyl chloride (2 equiv.) is added followed by DMF (1 drop). The reaction is allowed to stir for 2 hours and is then quenched with methanol. The reaction mixture is then concentrated yielding the desired methyl ester.

Methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-methyltetrahydrofuran-2-carboxylate



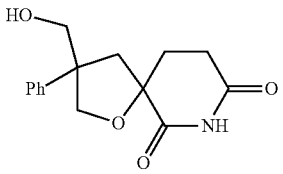
Methyl 4-((benzyloxy)methyl)-4-methyltetrahydrofuran-2-carboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-methyltetrahydrofuran-2-carboxylate.

3-(Hydroxymethyl)-3-methyl-1-oxa-7-azaspiro[4.5] decane-6,8-dione

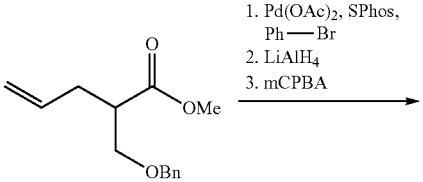


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-methyltetrahydrofuran-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 3-(hydroxymethyl)-3-methyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione.

Representative Example 6: 3-(Hydroxymethyl)-3-phenyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione



3-(Benzyloxy)-2-(oxiran-2-ylmethyl)-2-phenylpropan-1-ol



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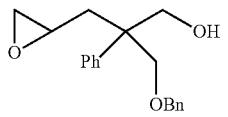
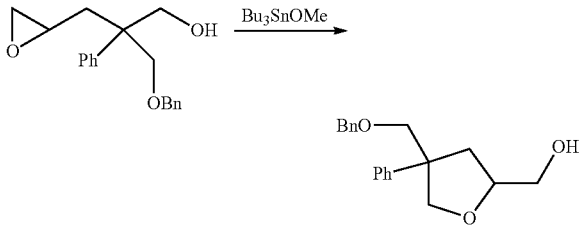


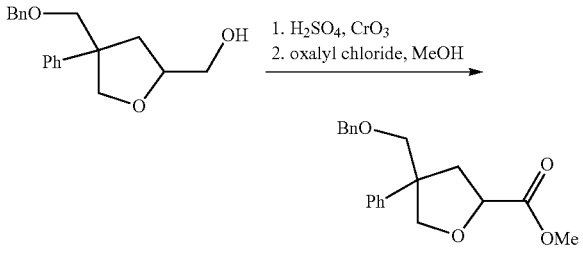
TMPZnCl.LiCl (1.30 M in THF, 1.5 equiv.) is added to a solution of 3-(benzyloxy)-2-methyl-2-(oxiran-2-ylmethyl) propan-1-ol (1 equiv.) in THF at room temperature. Pd(OAc)2 (2 mol %), SPhos (4 mol %) and aryl bromide (0.80 equiv.) are added to the reaction. The resulting mixture is stirred for 1 h at room temperature. The mixture is then quenched with saturated aqueous ammonium chloride solution and extracted with diethyl ether (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is then purified on silica to afford 3-(benzyloxy)-2-(oxiran-2-ylmethyl)-2-phenylpropan-1-ol (Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. Org. Lett. 2011, 13, 1690-1693.).

(4-((Benzyloxy)methyl)-4-phenyltetrahydrofuran-2-yl)methanol



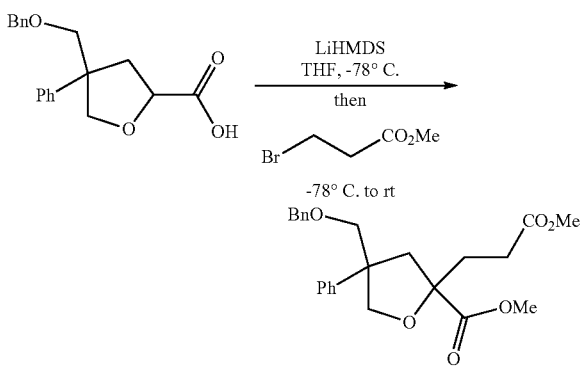
Procedure provided in Bats, J.; Moulines, J.; Pommier, J. C. Tetrahedron Lett. 1976, 26, 2249-2250, and Griffiths, G.; Stirling, C. J. M. Heterocycles, 1989, 28, 89-92.

Methyl 4-((benzyloxy)methyl)-4-phenyltetrahydrofuran-2-carboxylate



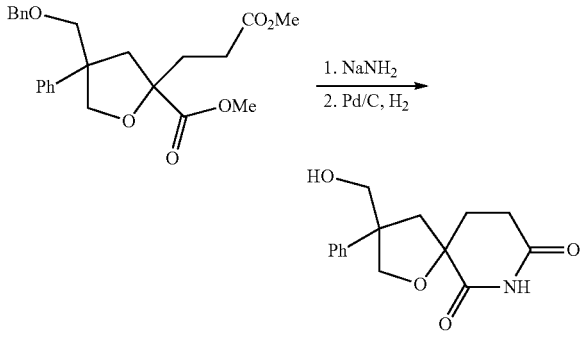
(4-((Benzyloxy)methyl)-4-phenyltetrahydrofuran-2-yl) methanol is dissolved in acetone. Jones' reagent is added slowly dropwise until the reaction was judged complete by TLC or LCMS analysis. Isopropanol is then added to quench the remaining chromium. The solids formed are filtered off and the filtrate is evaporated to dryness. The crude material is taken up in ethyl acetate, washed with water and then brine, dried over sodium sulfate and concentrated under reduced pressure to afford 4-((benzyloxy)methyl)-4-phenyltetrahydrofuran-2-carboxylic acid. The carboxylic acid is then dissolved in dichloromethane. Oxalyl chloride (2 equiv.) is added followed by DMF (1 drop). The reaction is allowed to stir for 2 hours and is then quenched with methanol. The reaction mixture is then concentrated yielding the desired methyl ester.

Methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-phenyltetrahydrofuran-2-carboxylate



Methyl 4-((benzyloxy)methyl)-4-phenyltetrahydrofuran-2-carboxylate (1 equiv.) is dissolved in dry tetrahydrofuran and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-phenyltetrahydrofuran-2-carboxylate.

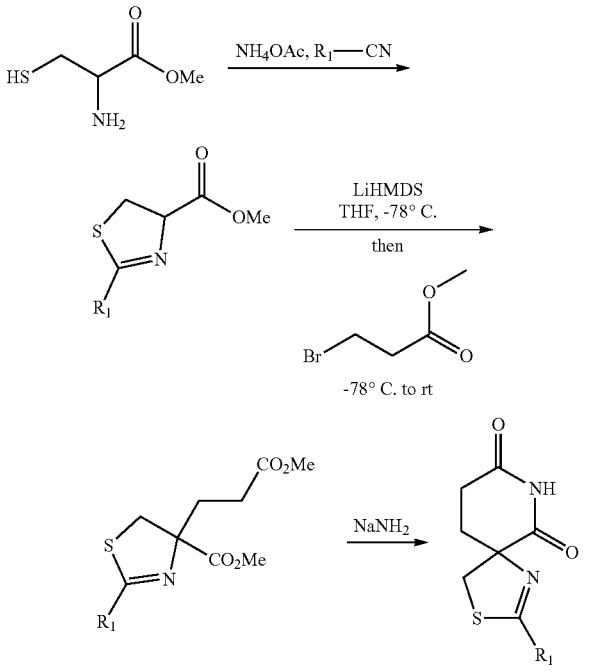
3-(Hydroxymethyl)-3-phenyl-1-oxa-7-azaspiro[4.5] decane-6,8-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 4-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-phenyltetrahydrofuran-2-carboxy-

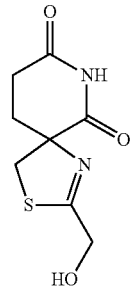
late in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 3-(hydroxymethyl)-3-phenyl-1-oxa-7-azaspiro[4.5]decane-6,8-dione.

General Scheme

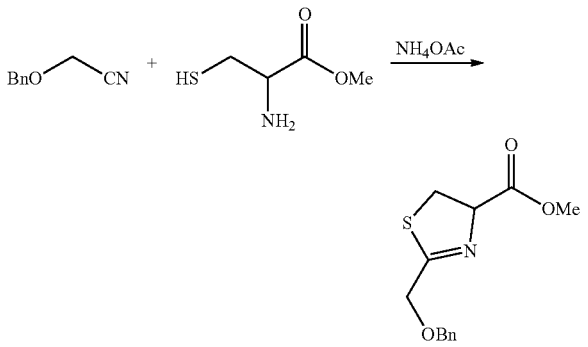


R_1 = H, Alk, Ar, HetAr

Representative Example 7: 2-(Hydroxymethyl)-3-thia-1,7-diazaspiro[4.5]dec-1-ene-6,8-dione

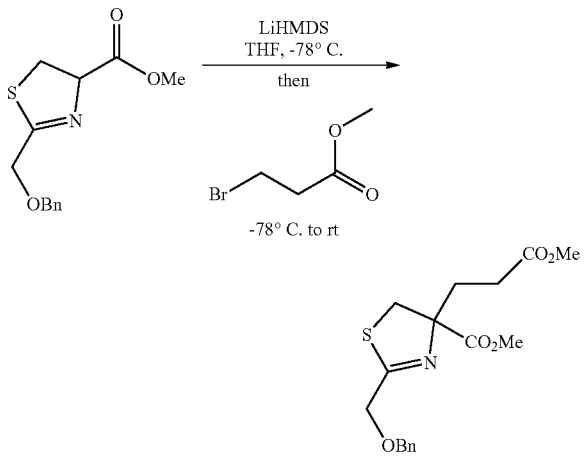


Methyl 2-((benzyloxy)methyl)-4,5-dihydrothiazole-4-carboxylate



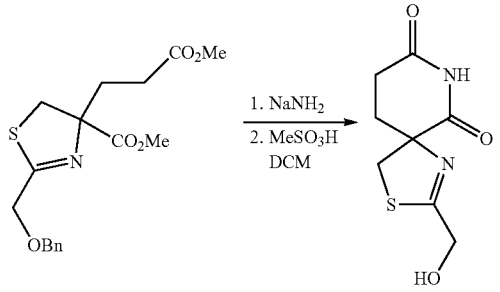
To a stirred solution of 2-(benzyloxy)acetonitrile (1 equiv.) and ammonium acetate (4 equiv.) in methanol is added cysteine hydrochloride and the mixture is stirred overnight at room temperature. The organic solvent is evaporated under reduced pressure and the residue is purified on silica (Kokotos, G.; et al., J. Med. Chem. 2014, 57, 7523-7535.).

Methyl-2-((benzyloxy)methyl)-4-(3-methoxy-3-oxo-propyl)-4,5-dihydrothiazole-4-carboxylate



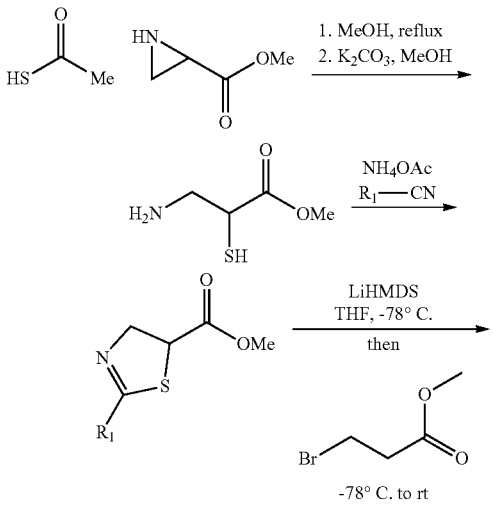
Methyl 2-((benzyloxy)methyl)-4,5-dihydrothiazole-4-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 2-((benzyloxy)methyl)-4-(3-methoxy-3-oxopropyl)-4,5-dihydrothiazole-4-carboxylate.

2-(Hydroxymethyl)-3-thia-1,7-diazaspiro [4.5] dec-1-ene-6,8-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 2-((benzyloxy)methyl)-4-(3-methoxy-3-oxopropyl)-4, 5-dihydrothiazole-4-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in DCM. Methanesulfonic acid (20 equiv.) is then added and the reaction is allowed to stir at room temperature until it is judged complete based on TLC or LCMS analysis. The mixture is then quenched with saturated aqueous sodium bicarbonate solution and diluted with DCM. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure (Haydon, D. J.; et al., J. Med. Chem. 2010, 53, 3927-3936.). The crude residue is then purified on silica to afford 2-(hydroxymethyl)-3-thia-1,7-diazaspiro [4.5]dec-1-ene-6,8-dione.

General Scheme:



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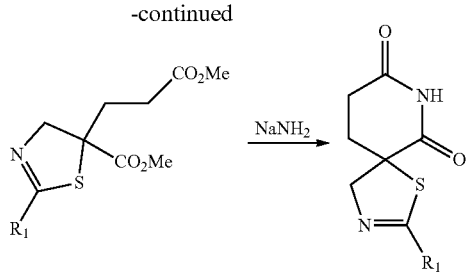
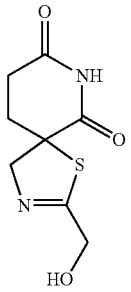
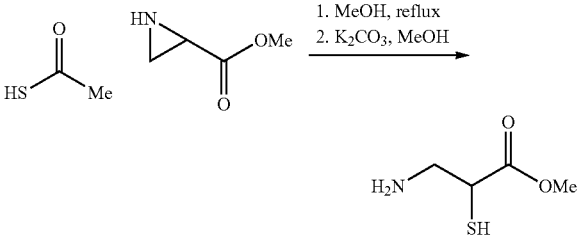


R_1 = H, Alk, Ar, HetAr

Representative Example 8: 2-(Hydroxymethyl)-1-thia-3,7-diazaspiro [4.5] dec-2-ene-6,8-dione

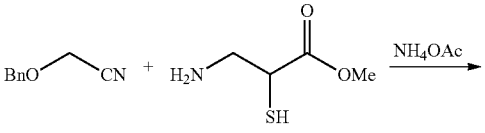


Methyl-3-amino-2-mercaptopropanoate



Methyl aziridine-2-carboxylate (1 equiv.) is dissolved in dry methanol. Thioacetic acid (1 equiv.) is added and the reaction is heated to reflux. Once the reaction is judged complete based on TLC or LCMS analysis, it is cooled to room temperature and concentrated under reduced pressure (U.S. Pat. No. 5,840,698 A). The crude residue is redissolved in methanol. Powdered potassium carbonate (5 equiv.) is added and the mixture is allowed to stir until the starting material is consumed. The mixture is concentrated under reduced pressure and used directly.

Methyl 2-((benzyloxy)methyl)-4,5-dihydrothiazole-5-carboxylate



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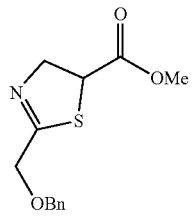
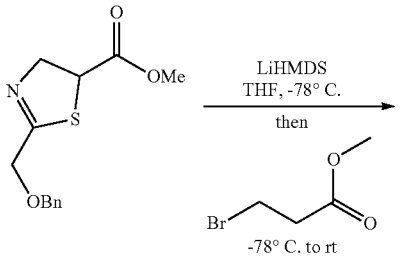
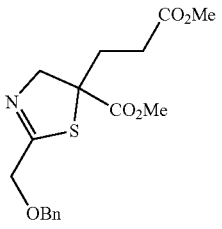


To a stirred solution of 2-(benzyloxy)acetonitrile (1 equiv.) and ammonium acetate (4 equiv.) in methanol is added methyl 3-amino-2-mercaptopropanoate and the mixture is stirred overnight at room temperature. The organic solvent is evaporated under reduced pressure and the residue is purified on silica (Kokotos, G.; et al., J. Med. Chem. 2014, 57, 7523-7535.).

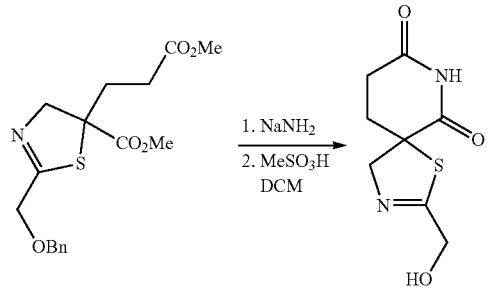
Methyl 2-((benzyloxy)methyl)-5-(3-methoxy-3-oxopropyl)-4,5-dihydrothiazole-5-carboxylate





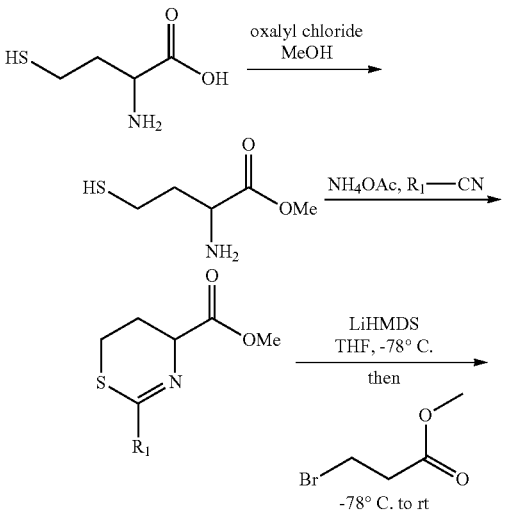
Methyl 2-((benzyloxy)methyl)-4,5-dihydrothiazole-5-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The reaction mixture is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 2-((benzyloxy)methyl)-5-(3-methoxy-3-oxopropyl)-4, 5-dihydrothiazole-5-carboxylate.

2-(Hydroxymethyl)-1-thia-3,7-diazaspiro [4.5] dec-2-ene-6,8-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 2-((benzyloxy)methyl)-5-(3-methoxy-3-oxopropyl)-4, 5-dihydrothiazole-5-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in DCM. Methanesulfonic acid (20 equiv.) is then added and the reaction is allowed to stir at room temperature until it is judged complete based on TLC or LCMS analysis. The mixture is then quenched with saturated aqueous sodium bicarbonate solution and diluted with DCM. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure (Haydon, D. J.; et al., J. Med. Chem. 2010, 53, 3927-3936.). The crude residue is then purified on silica to afford 2-(hydroxymethyl)-3-thia-1,7-diazaspiro [4.5]dec-1-ene-6,8-dione.

General Scheme:



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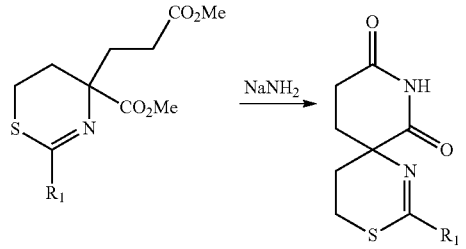
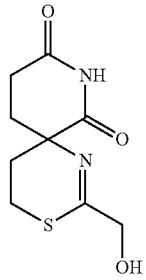
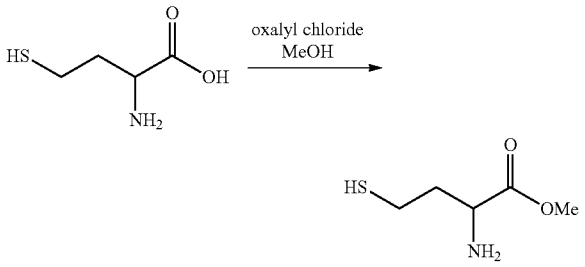


R_1 = H, Alk, Ar, HetAr

Representative Example 9: 2-(Hydroxymethyl)-3-thia-1,8-diazaspiro[5.5]undec-1-ene-7,9-dione

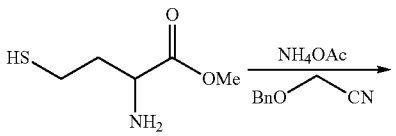


Methyl Homocysteine



Homocysteine then dissolved in dichloromethane. Oxalyl chloride (2 equiv.) is added followed by DMF (1 drop). The reaction is allowed to stir for 2 hours and is then quenched with methanol. The reaction mixture is then concentrated yielding the desired methyl ester.

Methyl 2-((benzyloxy)methyl)-5,6-dihydro-4H-1,3-thiazine-4-carboxylate



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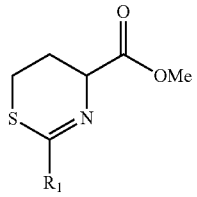
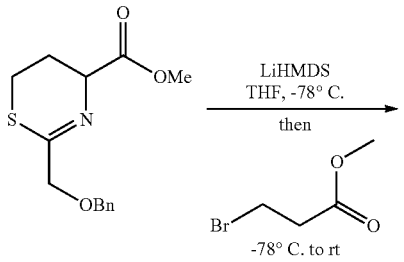
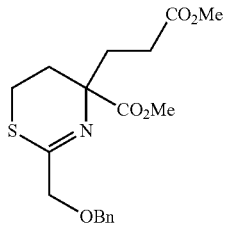


To a stirred solution of 2-(benzyloxy)acetonitrile (1 equiv.) and ammonium acetate (4 equiv.) in methanol is added methyl homocysteine and the mixture is stirred overnight at room temperature. The organic solvent is evaporated under reduced pressure and the residue is purified on silica (Kokotos, G.; et al., *J. Med. Chem.* 2014, 57, 7523-7535.).

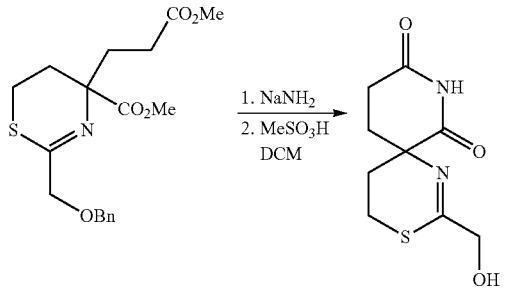
Methyl-2-((benzyloxy)methyl)-4-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-4-carboxylate





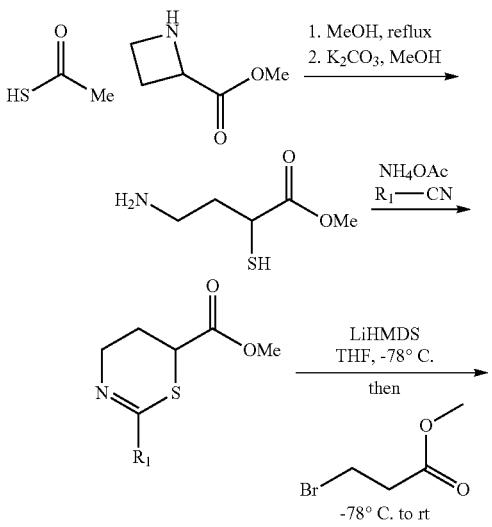
Methyl 2-((benzyloxy)methyl)-5,6-dihydro-4H-1,3-thiazine-4-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 2-((benzyloxy)methyl)-4-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-4-carboxylate.

2-(Hydroxymethyl)-3-thia-1,8-diazaspiro [5.5] undec-1-ene-7,9-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 2-((benzyloxy)methyl)-4-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-4-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in DCM. Methanesulfonic acid (20 equiv.) is then added and the reaction is allowed to stir at room temperature until it is judged complete based on TLC or LCMS analysis. The mixture is then quenched with saturated aqueous sodium bicarbonate solution and diluted with DCM. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure (Haydon, D. J.; et al., J. Med. Chem. 2010, 53, 3927-3936.). The crude residue is then purified on silica to afford 2-(hydroxymethyl)-3-thia-1,8-diazaspiro [5.5]undec-1-ene-7,9-dione.

General scheme:



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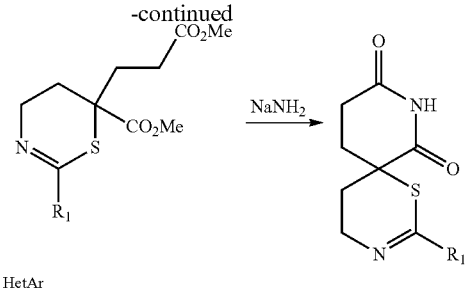
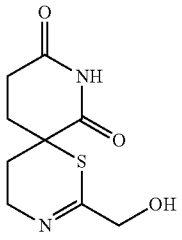
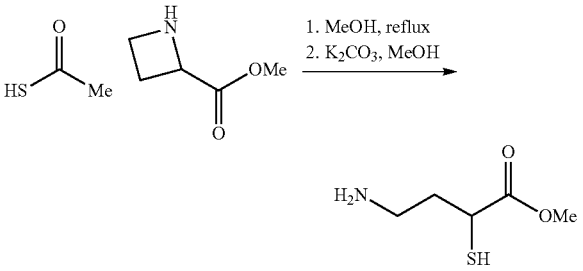


R_1 = H, Alk, Ar, HetAr

Representative Example 10: 2-(Hydroxymethyl)-1-thia-3,8-diazaspiro[5.5]undec-2-ene-7,9-dione

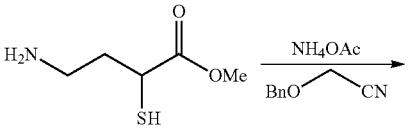


Methyl-4-amino-2-mercaptobutanoate



Methyl azetidine-2-carboxylate (1 equiv.) is dissolved in dry methanol. Thioacetic acid (1 equiv.) is added and the reaction is heated to reflux. Once the reaction is judged complete based on TLC or LCMS analysis, it is cooled to room temperature and concentrated under reduced pressure (U.S. Pat. No. 5,840,698 A and Hata, Y.; Watanabe, M. Tetrahedron, 1987, 43, 3881-3888.). The crude residue is redissolved in methanol. Powdered potassium carbonate (5 equiv.) is added and the mixture is allowed to stir until the starting material is consumed. The mixture is concentrated under reduced pressure and used directly.

Methyl-2-((benzyloxy)methyl)-5,6-dihydro-4H-1,3-thiazine-6-carboxylate



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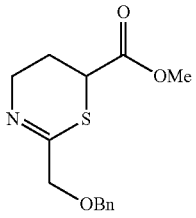
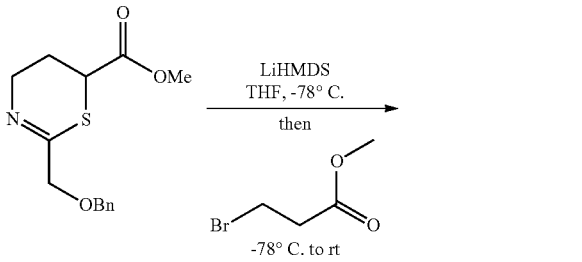
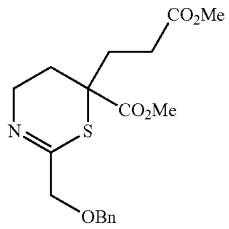


To a stirred solution of 2-(benzyloxy)acetonitrile (1 equiv.) and ammonium acetate (4 equiv.) in methanol is added methyl homocysteine and the mixture is stirred overnight at room temperature. The organic solvent is evaporated under reduced pressure and the residue is purified on silica (Kokotos, G.; et al., J. Med. Chem. 2014, 57, 7523-7535.).

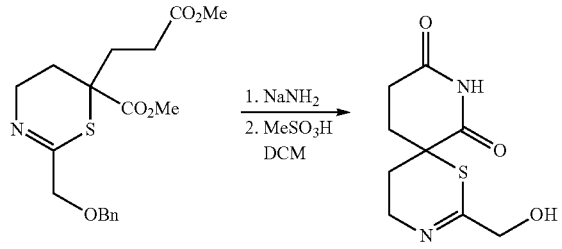
Methyl 2-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-6-carboxylate





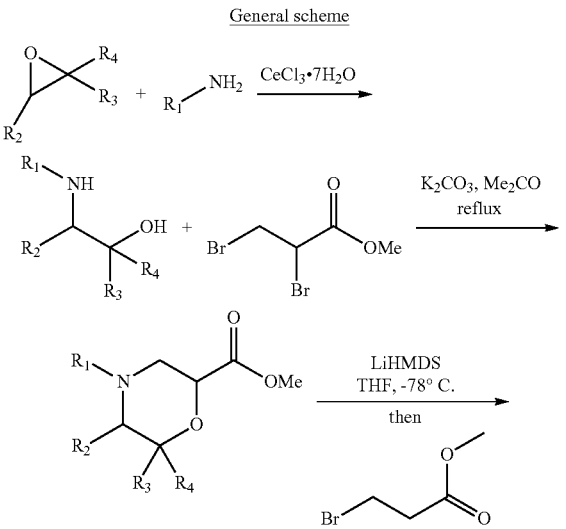
Methyl 2-((benzyloxy)methyl)-5,6-dihydro-4H-1,3-thiazine-6-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 2-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-6-carboxylate.

2-(Hydroxymethyl)-1-thia-3,8-diazaspiro [5.5] undec-2-ene-7,9-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 2-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-5,6-dihydro-4H-1,3-thiazine-6-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in DCM. Methanesulfonic acid (20 equiv.) is then added and the reaction is allowed to stir at room temperature until it is judged complete based on TLC or LCMS analysis. The mixture is then quenched with saturated aqueous sodium bicarbonate solution and diluted with DCM. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure (Haydon, D. J.; et al., J. Med. Chem. 2010, 53, 3927-3936.). The crude residue is then purified on silica to afford 2-(hydroxymethyl)-1-thia-3,8-diazaspiro [5.5]undec-2-ene-7,9-dione.

General scheme



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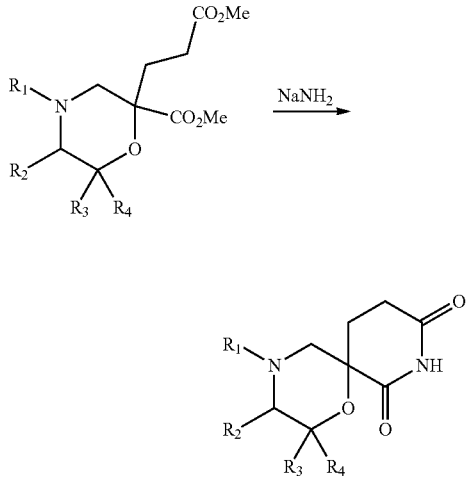
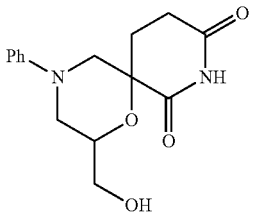
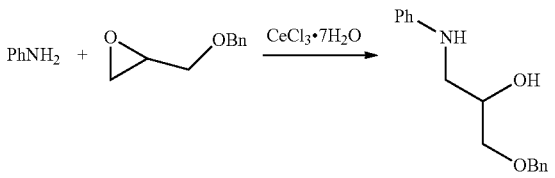


R_1 = H, Alk, HetAr
R_2 = H, Alk, HetAr
R_3 = H, Alk, HetAr
R_4 = H, Alk, HetAr

Representative Example 11: 2-(Hydroxymethyl)-4-phenyl-1-oxa-4,8-diazaspiro [5.5] undecane-7,9-dione

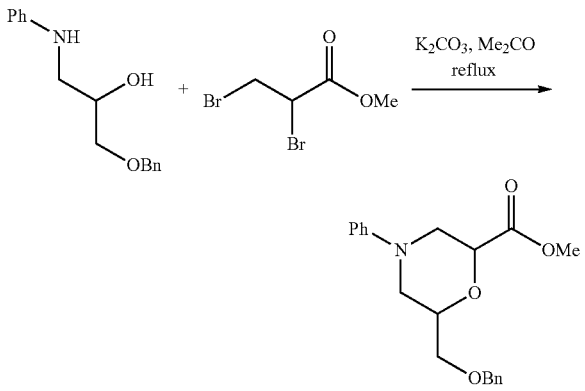


1-(Benzyloxy)-3-(phenylamino)propan-2-ol



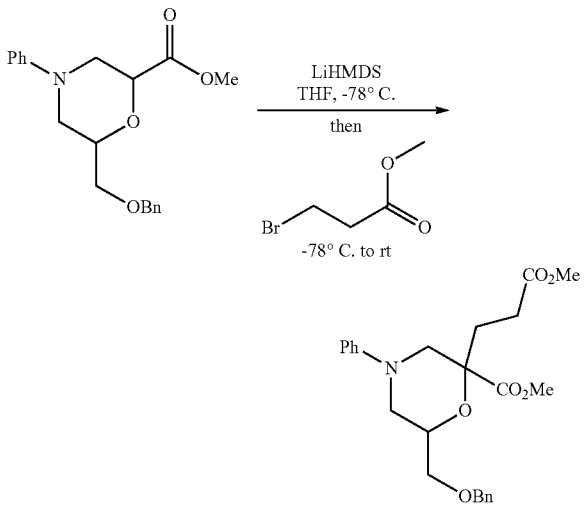
To a stirred mixture of epoxide (1 equiv.) in glycerine was added the amine (1 equiv.) and $CeCl_3*7H_2O$ (0.1 equiv.) at room temperature. The reaction mixture was stirred until the starting material was consumed as judged by TLC or LCMS analysis. The reaction mixture was then extracted with ethyl acetate (3×) and the combined organic layers were washed with water (2×) and brine before drying over sodium sulfate and concentrating under reduced pressure. The crude product was purified on silica to afford the ethanolamine derivative (Narsaiah, A. V.; Wadavrao, S. B.; Reddy, A. R.; Yadav, J. S.; Synthesis, 2011, 3, 485-489.).

Methyl 6-((benzyloxy)methyl)-4-phenylmorpholine-2-carboxylate



A mixture of methyl 2,3-dibromopropionate (1.2 equiv.) ethanolamine derivative (1 equiv.) and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired morpholine adduct (PCT Int. Appl., 20101394811).

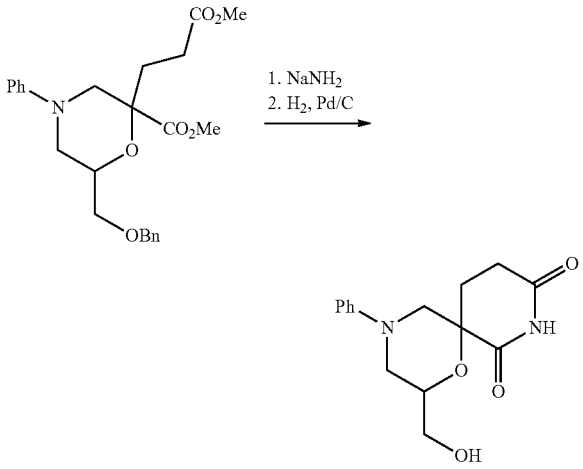
Methyl 6-((benzyloxy)methyl)-2-(3-methoxy-3-oxo-propyl)-4-phenylmorpholine-2-carboxylate



Methyl 6-((benzyloxy)methyl)-4-phenylmorpholine-2-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with

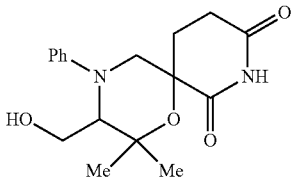
brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 6-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-phenylmorpholine-2-carboxylate.

2-(Hydroxymethyl)-4-phenyl-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione

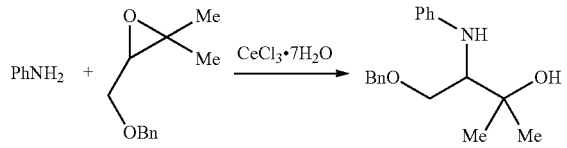


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 6-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-4-phenylmorpholine-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 2-(hydroxymethyl)-4-phenyl-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione.

Representative Example 12: 3-(Hydroxymethyl)-2,2-dimethyl-4-phenyl-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione

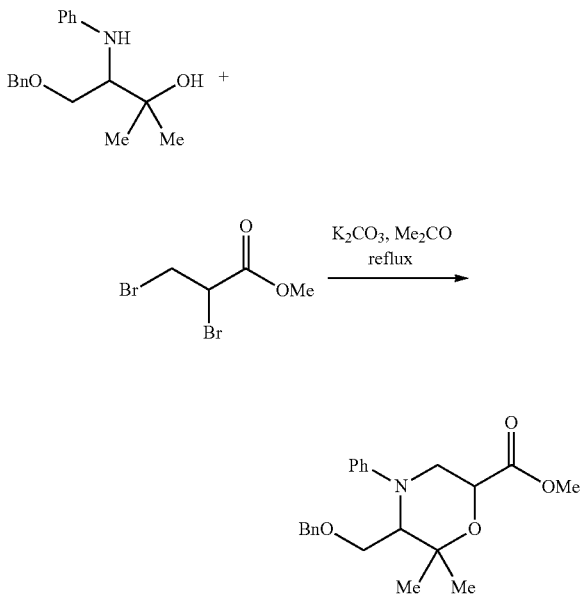


4-(Benzyloxy)-2-methyl-3-(phenylamino)butan-2-ol



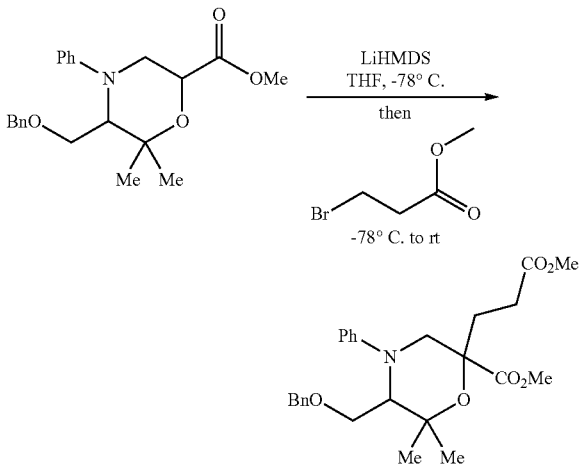
To a stirred mixture of epoxide (1 equiv.) in glycerine was added the amine (1 equiv.) and $CeCl_3.7H_2O$ (0.1 equiv.) at room temperature. The reaction mixture was stirred until the starting material was consumed as judged by TLC or LCMS analysis. The reaction mixture was then extracted with ethyl acetate (3×) and the combined organic layers were washed with water (2×) and brine before drying over sodium sulfate and concentrating under reduced pressure. The crude product was purified on silica to afford the ethanolamine derivative (Narsaiah, A. V.; Wadavrao, S. B.; Reddy, A. R.; Yadav, J. S.; Synthesis, 2011, 3, 485-489.).

Methyl 5-((benzyloxy)methyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate



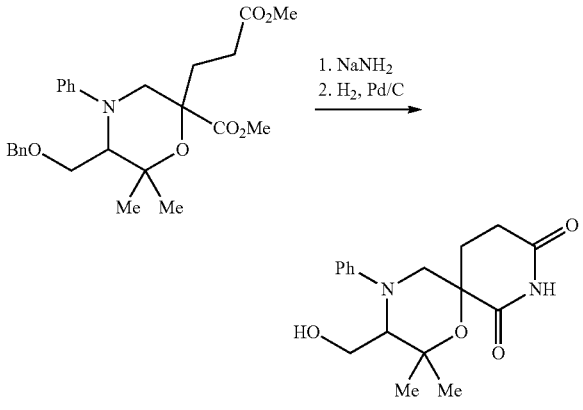
A mixture of methyl 2,3-dibromopropionate (1.2 equiv.) ethanolamine derivative (1 equiv.) and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired morpholine adduct (PCT Int. Appl., 2010139481).

Methyl 5-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate



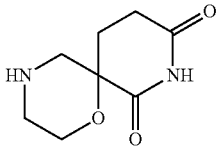
Methyl 5-((benzyloxy)methyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 5-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate.

3-(Hydroxymethyl)-2,2-dimethyl-4-phenyl-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione

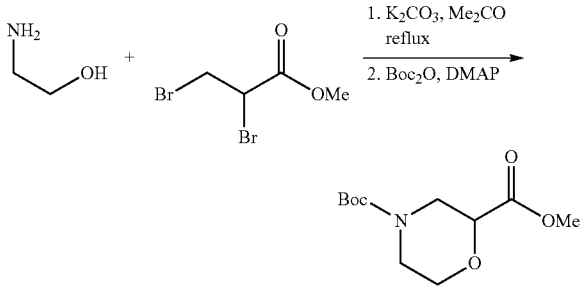


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 5-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 3-(hydroxymethyl)-2,2-dimethyl-4-phenyl-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione.

Representative Example 13: 1-Oxa-4,8-diazaspiro[5.5]undecane-7,9-dione

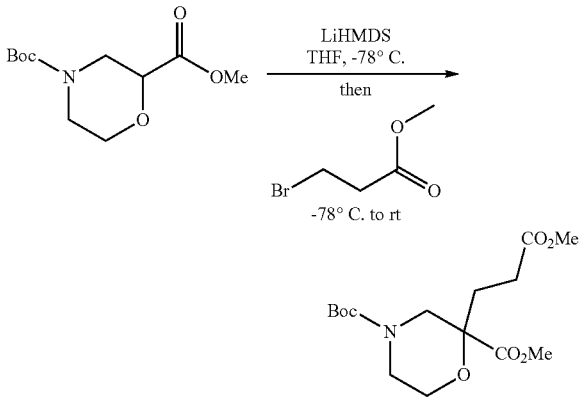


4-(tert-Butyl) 2-methyl morpholine-2,4-dicarboxylate



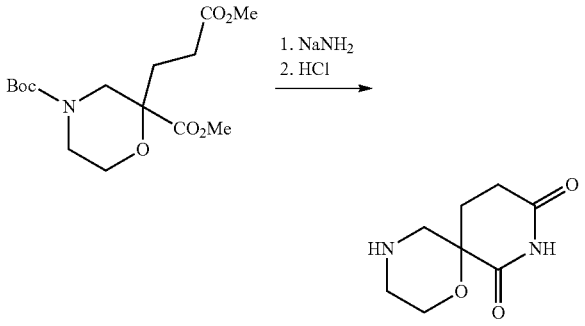
A mixture of methyl 2,3-dibromopropionate (1.2 equiv.) ethanolamine derivative (1 equiv.) and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired morpholine adduct (PCT Int. Appl., 2010139481). The free morpholine adduct is then dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting crude material is purified on silica to afford 4-(tert-butyl) 2-methyl morpholine-2,4-dicarboxylate.

4-(tert-Butyl) 2-methyl 2-(3-methoxy-3-oxopropyl) morpholine-2,4-dicarboxylate



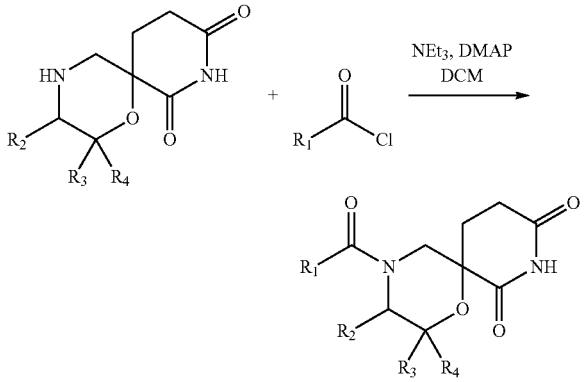
4-(t-Butyl) 2-methyl morpholine-2,4-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 4-(tert-butyl) 2-methyl 2-(3-methoxy-3-oxopropyl)morpholine-2,4-dicarboxylate.

1-Oxa-4,8-diazaspiro [5.5] undecane-7,9-dione



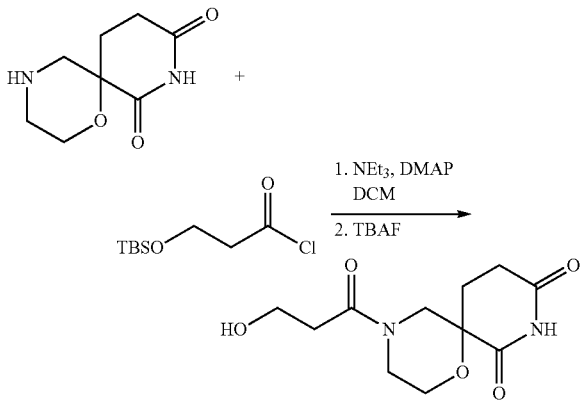
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 5-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The Boc-protected morpholine adduct is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude material is purified on silica to afford 1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione.

General Scheme



R_1 = H, Alk, Ar, HetAr
R_2 = H, Alk, Ar, HetAr
R_3 = H, Alk, Ar, HetAr
R_4 = H, Alk, Ar, HetAr

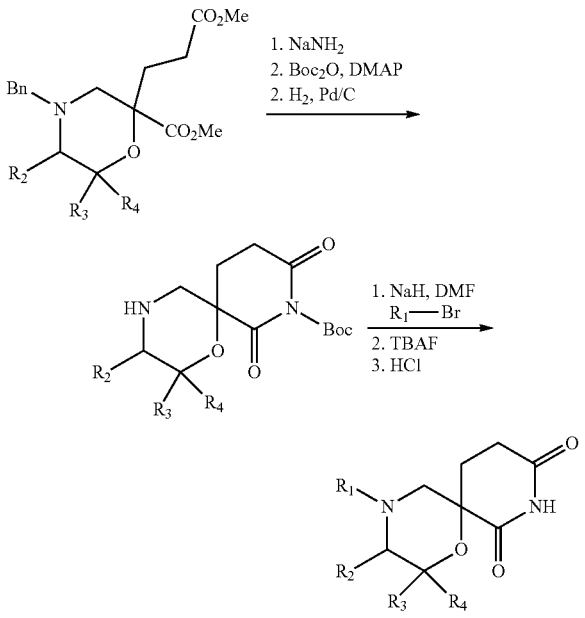
Representative Example 14: 4-(3-Hydroxypropanoyl)-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione



1-Oxa-4,8-diazaspiro[5.5]undecane-7,9-dione (1 equiv.) is dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic

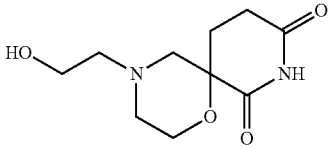
layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 4-(3-hydroxypropanoyl)-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione.

General Scheme

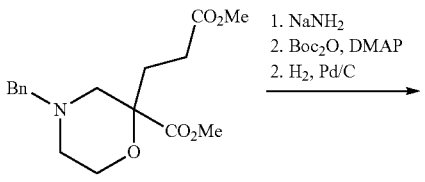


R_1 = Alk, Ar, HetAr
R_2 = H, Alk, Ar, HetAr
R_3 = H, Alk, Ar, HetAr
R_4 = H, Alk, Ar, HetAr

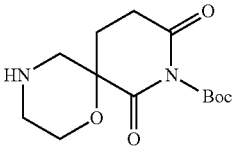
Representative Example 15: 4-(2-Hydroxyethyl)-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione



tert-Butyl 7,9-dioxo-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate

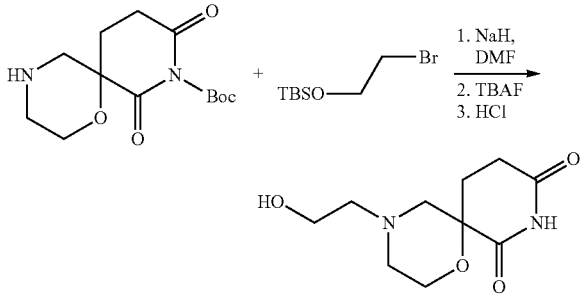


-continued



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 5-((benzyloxy)methyl)-2-(3-methoxy-3-oxopropyl)-6,6-dimethyl-4-phenylmorpholine-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The free morpholine adduct is then dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting crude material is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding tert-butyl 7,9-dioxo-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate.

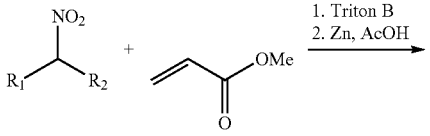
4-(2-Hydroxyethyl)-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione



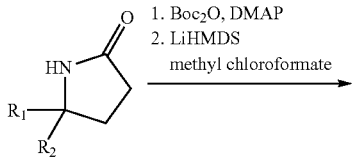
7-Benzyl-2,7-diazaspiro[4.5]decane-3,6,8-trione (1 equiv.) is dissolved in DMF and added to a suspension of sodium hydride (1.05 equiv., 60% dispersion in mineral oil) and potassium iodide (1 equiv.) in DMF. The mixture is stirred for 90 minutes while warming to room temperature. (2-bromoethoxy)(tert-butyl)dimethylsilane (1.1 equiv.) in a solution of DMF is then added to the reaction mixture which is stirred at 55° C. The mixture is stirred until the starting material is consumed as judged by TLC or LCMS analysis. The volatiles are then removed under reduced pressure and the residue is redissolved in ethyl acetate and washed with water. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic

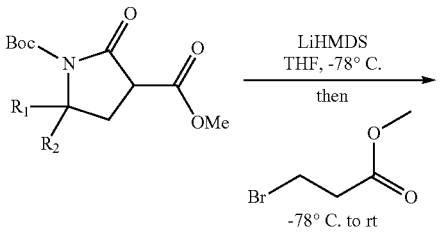
layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The Boc-protected imide is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure to afford 4-(2-hydroxyethyl)-1-oxa-4,8-diazaspiro[5.5]undecane-7,9-dione.

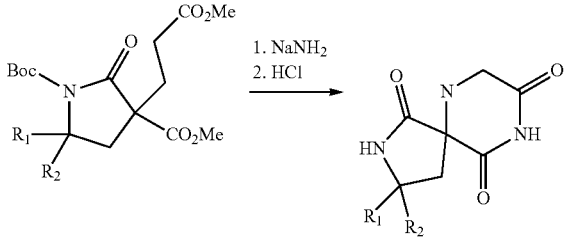
General Scheme



Conjugate addition of nitro alkane; reductive lactam formation: PCT Int. Appl., 2007025780, 08 Mar 2007

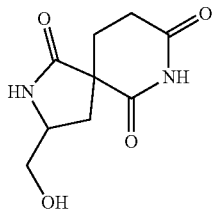




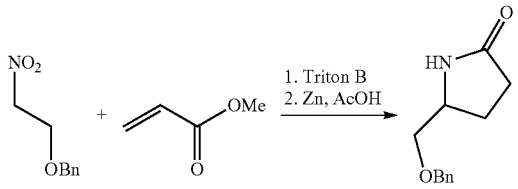


R_1 = H, Alk, Ar, HetAr
R_2 = H, Alk, Ar, HetAr

Representative Example 16: 3-(Hydroxymethyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione

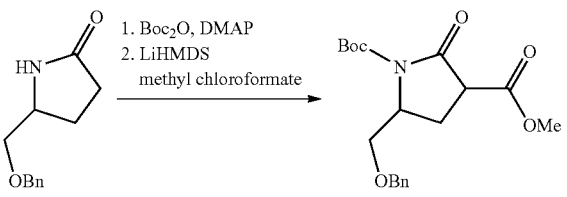


5-((Benzyloxy)methyl)pyrrolidin-2-one



((2-Nitroethoxy)methyl)benzene (1 equiv.) is dissolved in isopropanol. Ethyl acrylate (5 equiv.) is added followed by Triton-B (1.5 equiv.). The solution is stirred at room temperature until the starting material is consumed as judged by TLC or LCMS analysis. The reaction is then poured into ice water and neutralized with 1.0 M HCl solution. The mixture is then extracted with ethyl acetate (3×) and the combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting crude material is dissolved in acetic acid and zinc powder (10 equiv.) is added. The mixture is heated to 110° C. for 6 hours, and then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, then saturated aqueous sodium bicarbonate solution, then brine. The organic layer was then dried over sodium sulfate and concentrated under reduced pressure. The material was then purified on silica to provide the desired lactam (PCT Int. Appl., 2007025780).

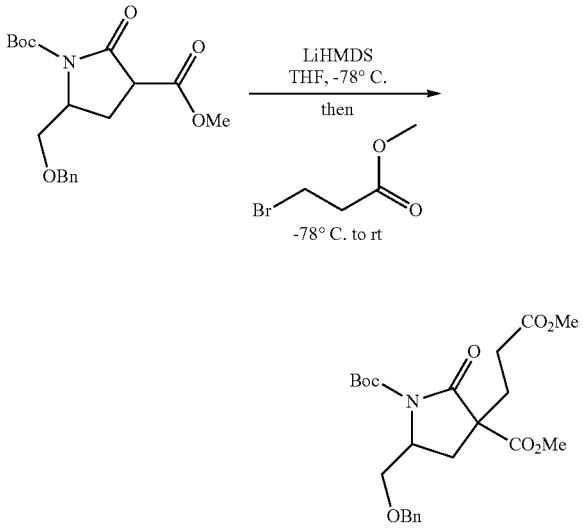
1-(tert-Butyl) 3-methyl 5-((benzyloxy)methyl)-2-oxopyrrolidine-1,3-dicarboxylate



The lactam (1 equiv.) is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined

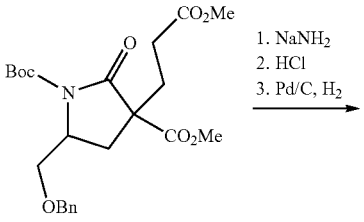
organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting crude material is then dissolved in THF and cooled to −78° C. LDA (1.2 equiv.) is added and the solution is allowed to stir for 30 minutes. Methyl chloroformate (1.2 equiv.) is then added and the mixture is allowed to warm gradually to room temperature and stir until the starting material is consumed as judged by TLC or LCMS analysis. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 1-(tert-butyl) 3-methyl 5-((benzyloxy)methyl)-2-oxopyrrolidine-1,3-dicarboxylate.

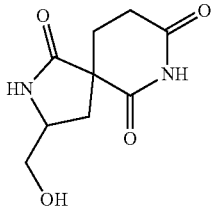
1-(tert-Butyl) 3-methyl 5-((benzyloxy)methyl)-3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate



1-(t-Butyl) 3-methyl 5-((benzyloxy)methyl)-2-oxopyrrolidine-1,3-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 1-(tert-butyl) 3-methyl 5-((benzyloxy)methyl)-3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate.

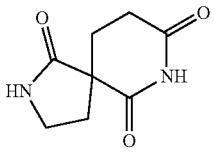
3-(Hydroxymethyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione



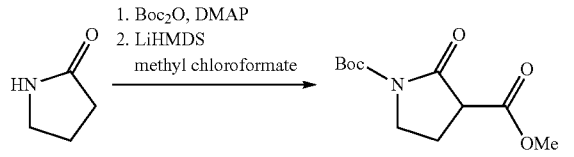


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 1-(tert-butyl) 3-methyl 5-((benzyloxy)methyl)-3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The Boc-protected lactam is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure. The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 3-(hydroxymethyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione.

Representative Example 17:
2,7-Diazaspiro[4.5]decane-1,6,8-trione

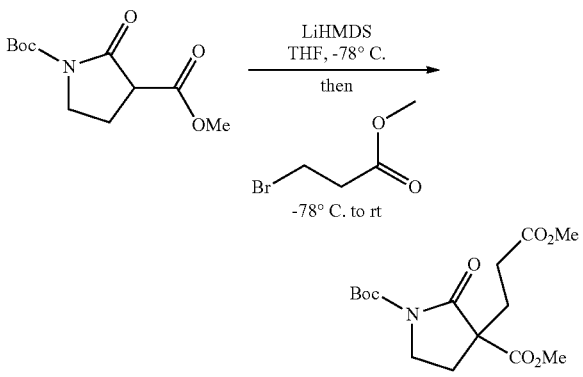


1-(t-Butyl) 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate



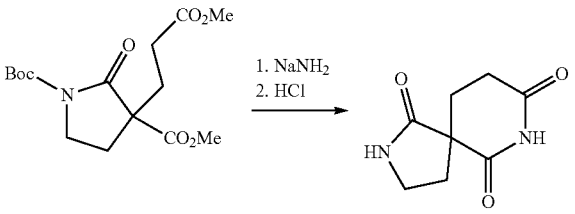
The lactam (1 equiv.) is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting crude material is then dissolved in THF and cooled to −78° C. LDA (1.2 equiv.) is added and the solution is allowed to stir for 30 minutes. Methyl chloroformate (1.2 equiv.) is then added and the mixture is allowed to warm gradually to room temperature and stir until the starting material is consumed as judged by TLC or LCMS analysis. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 1-(tert-butyl) 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate.

1-(t-Butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate



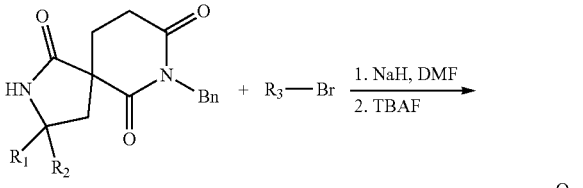
1-(t-Butyl) 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate.

2,7-Diazaspiro[4.5]decane-1,6,8-trione



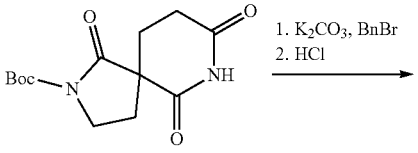
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-2-oxopyrrolidine-1,3-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The Boc-protected lactam is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure. The crude material is then purified on silica to provide 2,7-diazaspiro[4.5]decane-1,6,8-trione.

General Scheme

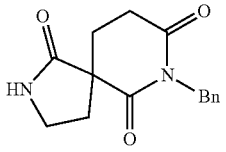


R_1 = H, Alk, Ar, HetAr
R_2 = H, Alk, Ar, HetAr
R_3 = Alk

7-Benzyl-2,7-diazaspiro[4.5]decane-1,6,8-trione

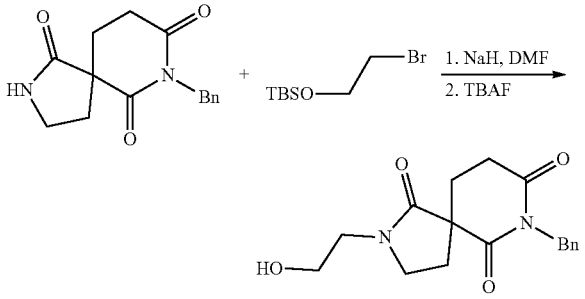


-continued



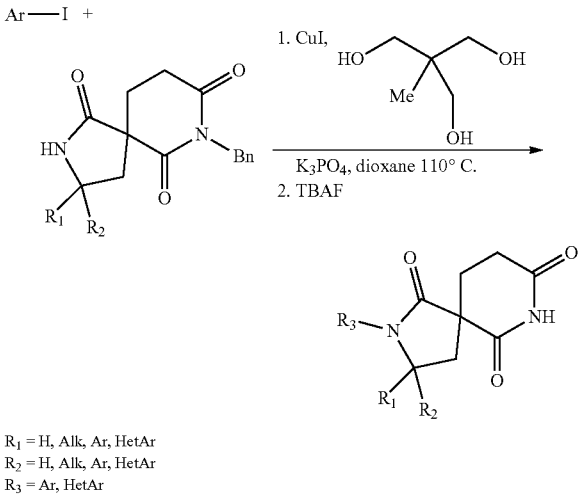
Glutarimide (1 equiv.) was dissolved in acetone. Potassium carbonate (2 equiv.) is added followed by benzyl bromide. The reaction mixture is heated to 50° C. When the starting material is consumed as judged by TLC or LCMS analysis, the reaction was cooled to room temperature. The acetone was evaporated and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was then washed with brine, dried over sodium sulfate and concentrated under reduced pressure (PCT Int. Appl., 2011144584). The Boc-protected lactam is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure. The crude material is then purified on silica to provide 7-benzyl-2,7-diazaspiro[4.5]decane-1,6,8-trione.

7-Benzyl-2-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione



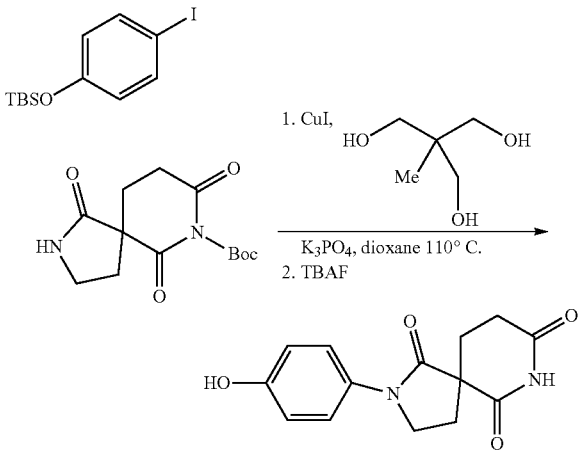
7-Benzyl-2,7-diazaspiro[4.5]decane-1,6,8-trione (1 equiv.) is dissolved in DMF and added to a suspension of sodium hydride (1.05 equiv., 60% dispersion in mineral oil) and potassium iodide (1 equiv.) in DMF. The mixture is stirred for 90 minutes while warming to room temperature. (2-bromoethoxy)(tert-butyl)dimethylsilane (1.1 equiv.) in a solution of DMF is then added to the reaction mixture which is stirred at 55° C. The mixture is stirred until the starting material is consumed as judged by TLC or LCMS analysis. The volatiles are then removed under reduced pressure and the residue is redissolved in ethyl acetate and washed with water. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 7-benzyl-2-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione.

General scheme



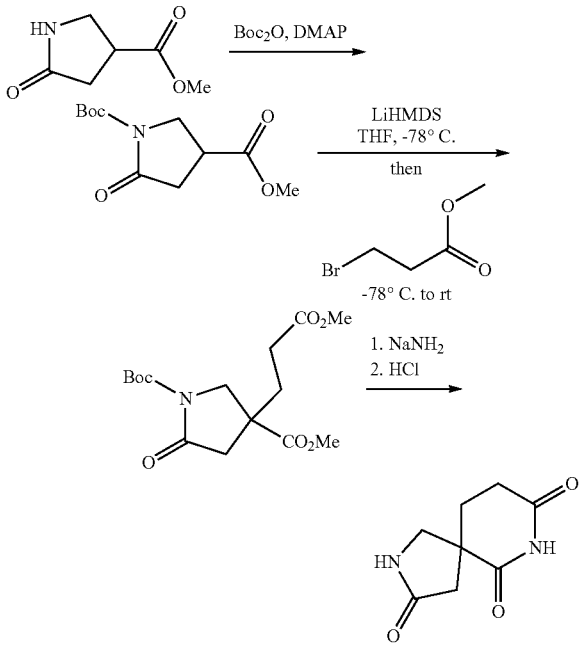
R_1 = H, Alk, Ar, HetAr
R_2 = H, Alk, Ar, HetAr
R_3 = Ar, HetAr

2-(4-Hydroxyphenyl)-2,7-diazaspiro[4.5]decane-1,6,8-trione

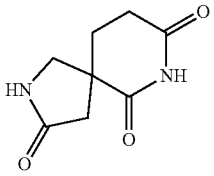


Cesium carbonate (2 equiv.), copper (I) iodide (0.1 equiv.) and 1,1,1-tris(hydroxymethyl)ethane (0.1 equiv.) is added to a screw-capped test tube with a septum. The tube is evacuated and backfilled with nitrogen three times. Dioxane and DMF (9:1) are added to the tube. tert-butyl(4-iodophenoxy) dimethylsilane (1 equiv.) and 7-benzyl-2,7-diazaspiro[4.5] decane-3,6,8-trione (1.2 equiv.) are added as a solution in dioxane. The reaction vessel is sealed and heated to 110° C. for 24 h. The reaction is then allowed to cool to room temperature and filtered through Celite® with ethyl acetate. The resulting filtrate is concentrated and the crude material is then purified on silica to afford 2-(4-hydroxyphenyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione (Chen, Y., -J.; Chen, H.-H.; Org. Lett. 2006, 8, 5609-5612.; Bregman, H.; et al.; J. Med. Chem. 2013, 56, 4320-4342.).

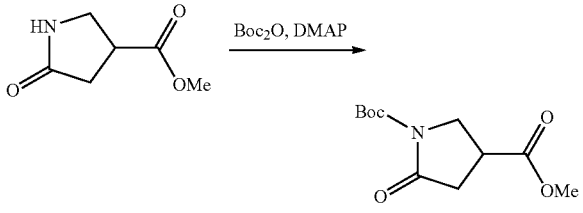
General scheme



Representative Example 18:
2,7-Diazaspiro[4.5]decane-3,6,8-trione

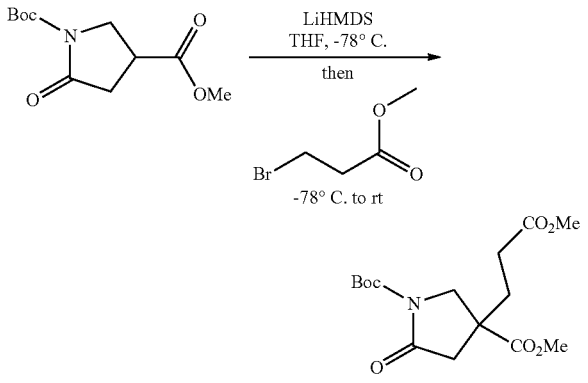


1-(t-Butyl) 3-methyl
5-oxopyrrolidine-1,3-dicarboxylate



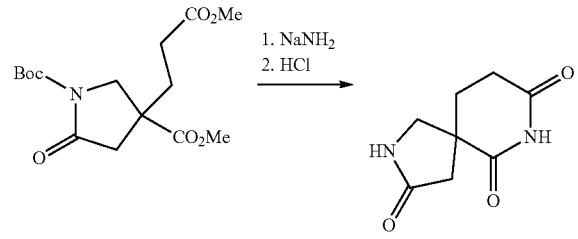
The lactam (1 equiv.) is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating to provide 1-(tert-butyl) 3-methyl 5-oxopyrrolidine-1,3-dicarboxylate.

1-(t-Butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-5-oxopyrrolidine-1,3-dicarboxylate



1-(t-Butyl) 3-methyl 5-oxopyrrolidine-1,3-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-5-oxopyrrolidine-1,3-dicarboxylate.

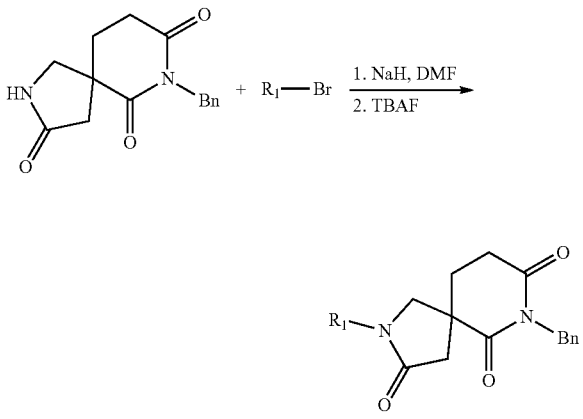
2,7-Diazaspiro[4.5]decane-3,6,8-trione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 1-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-5-oxopyrrolidine-1,3-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography (Synthesis, 1985, (4), 402-403.). The Boc-protected lactam is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated

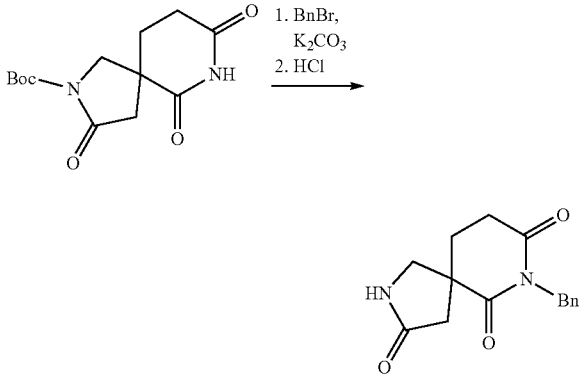
under reduced pressure. The crude material is then purified on silica to provide 2,7-diazaspiro[4.5]decane-3,6,8-trione.

General scheme



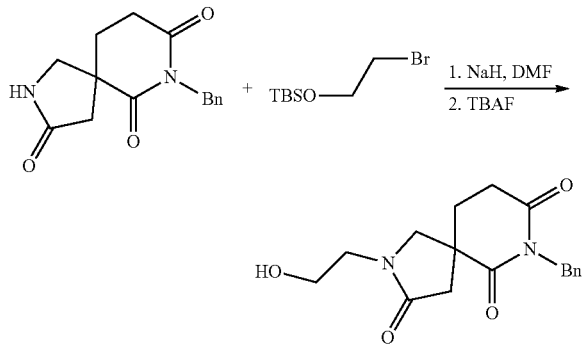
R_1 = Alk

7-Benzyl-2,7-diazaspiro[4.5]decane-3,6,8-trione



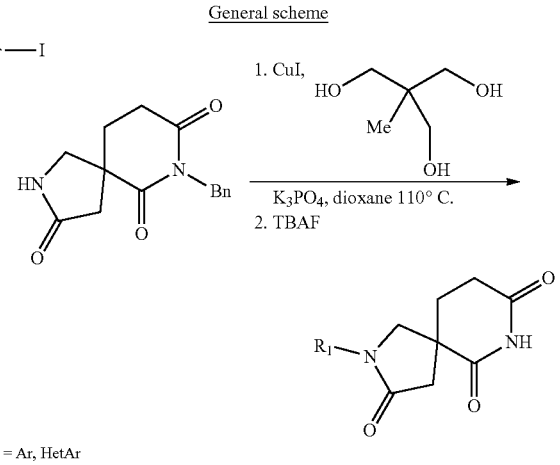
Glutarimide (1 equiv.) was dissolved in acetone. Potassium carbonate (2 equiv.) is added followed by benzyl bromide. The reaction mixture is heated to 50° C. When the starting material is consumed as judged by TLC or LCMS analysis, the reaction was cooled to room temperature. The acetone was evaporated and the residue was dissolved in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was then washed with brine, dried over sodium sulfate and concentrated under reduced pressure (PCT Int. Appl., 2011144584). The Boc-protected lactam is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure. The crude material is then purified on silica to provide 7-benzyl-2,7-diazaspiro[4.5]decane-3,6,8-trione.

7-Benzyl-2-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione



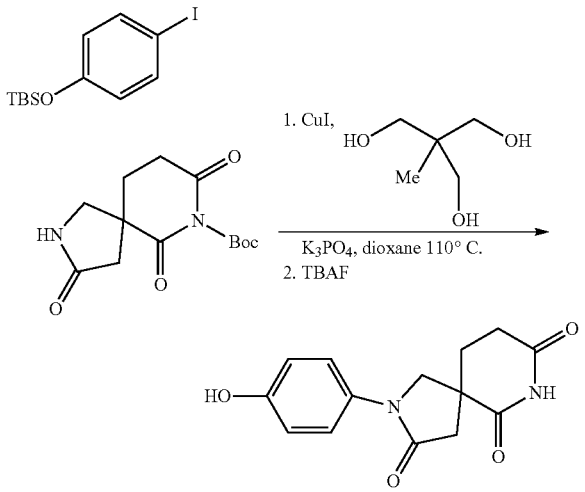
7-Benzyl-2,7-diazaspiro[4.5]decane-3,6,8-trione (1 equiv.) is dissolved in DMF and added to a suspension of sodium hydride (1.05 equiv., 60% dispersion in mineral oil) and potassium iodide (1 equiv.) in DMF. The mixture is stirred for 90 minutes while warming to room temperature. (2-bromoethoxy)(tert-butyl)dimethylsilane (1.1 equiv.) in a solution of DMF is then added to the reaction mixture which is stirred at 55° C. The mixture is stirred until the starting material is consumed as judged by TLC or LCMS analysis. The volatiles are then removed under reduced pressure and the residue is redissolved in ethyl acetate and washed with water. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude residue is then dissolved in anhydrous THF. TBAF (1.2 equiv.) is then added and the reaction mixture stirred at room temperature until the starting material was consumed as judged by TLC or LCMS analysis. The mixture was then poured into water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating under reduced pressure to afford 7-benzyl-2-(2-hydroxyethyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione.

General scheme



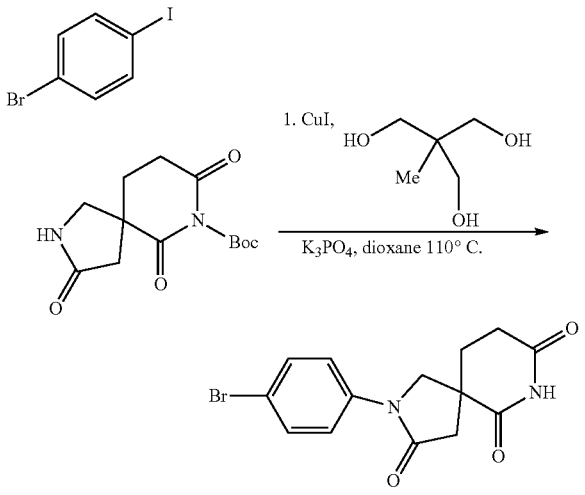
R_1 = Ar, HetAr

2-(4-Hydroxyphenyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione



Cesium carbonate (2 equiv.), copper (I) iodide (0.1 equiv.) and 1,1,1-tris(hydroxymethyl)ethane (0.1 equiv.) is added to a screw-capped test tube with a septum. The tube is evacuated and backfilled with nitrogen three times. Dioxane and DMF (9:1) are added to the tube. tert-butyl(4-iodophenoxy) dimethylsilane (1 equiv.) and 7-benzyl-2,7-diazaspiro[4.5] decane-3,6,8-trione (1.2 equiv.) are added as a solution in dioxane. The reaction vessel is sealed and heated to 110° C. for 24 h. The reaction is then allowed to cool to room temperature and filtered through Celite® with ethyl acetate. The resulting filtrate is concentrated and the crude material is then purified on silica to afford 2-(4-hydroxyphenyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione (Chen, Y., -J.; Chen, H.-H.; Org. Lett. 2006, 8, 5609-5612.; Bregman, H.; et al.; J. Med. Chem. 2013, 56, 4320-4342.).

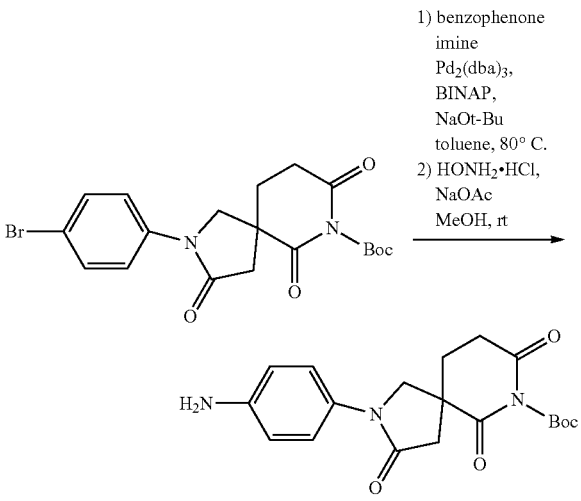
2-(4-Bromophenyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione



Cesium carbonate (2 equiv.), copper (I) iodide (0.1 equiv.) and 1,1,1-tris(hydroxymethyl)ethane (0.1 equiv.) is added to a screw-capped test tube with a septum. The tube is evacuated and backfilled with nitrogen three times. Dioxane and DMF (9:1) are added to the tube. 1-bromo-4-iodobenzene (1 equiv.) and 7-benzyl-2,7-diazaspiro[4.5]decane-3,6,8-trione (1.2 equiv.) are added as a solution in dioxane. The reaction vessel is sealed and heated to 110° C. for 24 h. The reaction is then allowed to cool to room temperature and filtered through Celite® with ethyl acetate. The resulting filtrate is concentrated and the crude material is then purified on silica to afford 2-(4-bromophenyl)-2,7-diazaspiro[4.5]decane-3,6,8-trione (Chen, Y., -J.; Chen, H.-H.; Org. Lett. 2006, 8, 5609-5612.; Bregman, H.; et al.; J. Med. Chem. 2013, 56, 4320-4342.).

Intermediate Functionalization in Preparation for Linker Installation

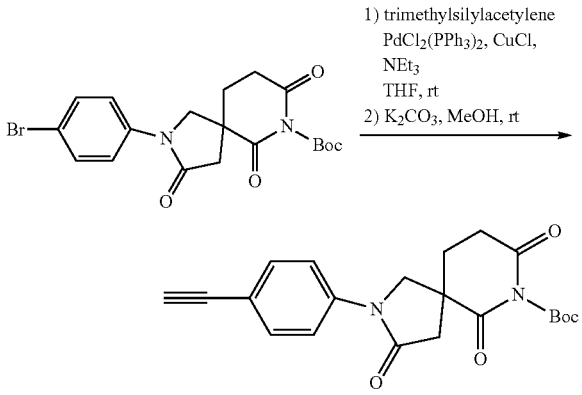
t-Butyl 2-(4-aminophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with tert-butyl 2-(4-bromophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.), benzophenone imine (1.2 equiv.), tris(dibenzylideneacetone)dipalladium(0) (1 mol %), BINAP (3 mol %) and sodium tert-butoxide and purged by cycling between nitrogen and vacuum 3 times. Toluene is added and the reaction is heated at 80° C. for 18 hours. Ethyl acetate is added and the solids separated by filtration through a plug of Celite®. The filtrate is concentrated and the residue is purified by chromatography to provide tert-butyl 2-(4-((diphenylmethylene)amino)phenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

A reaction vessel is charged with tert-butyl 2-(4-((diphenylmethylene)amino)phenyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decane-7-carboxylate (1 equiv.) and dissolved in MeOH. Hydroxylamine hydrochloride (1.8 equiv.) and sodium acetate (2.4 equiv.) are added and the reaction mixed at ambient temperature for 1 hour. The reaction is quenched by addition of 0.1M aq. NaOH solution and the resultant mixture extracted with ethyl acetate. The combined organic layer is washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-aminophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (PCT Int. Appl., 2015002230, 8 Jan. 2015).

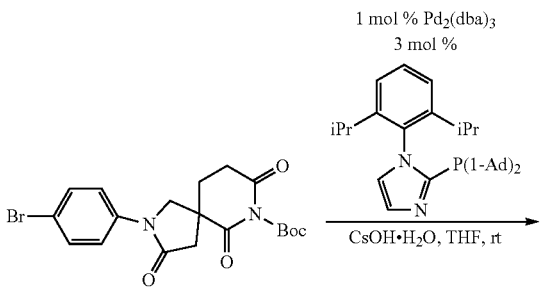
tert-Butyl 2-(4-ethynylphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with bis(triphenylphosphine) palladium(II) chloride (2 mol %), copper(I) iodide (4 mol %) and tert-butyl 2-(4-bromophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.). The reaction atmosphere is cycled between nitrogen and vacuum 3 times then triethylamine (1.55 equiv.) and trimethylsilylacetylene (1.25 equiv.) are added and the reaction is mixed for 24 hours. When the starting materials are consumed, the reaction is diluted with ethyl acetate and filtered through a plug of Celite®. The filtrate is concentrated and the residue is purified by silica gel chromatography to provide tert-butyl 3,6,8-trioxo-2-(4-((trimethylsilyl)ethynyl)phenyl)-2,7-diazaspiro[4.5] decane-7-carboxylate. (Org. Lett. 2014, 16(24), 6302)

A reaction vessel is charged with tert-butyl 2,6-dioxo-3-(4-((trimethylsilyl)ethynyl)phenyl)piperidine-1-carboxylate (1 equiv.), potassium carbonate (4 equiv.) and MeOH. The reaction is mixed at ambient temperature for 8 hours then concentrated. The residue is diluted with water and ethyl acetate. The aqueous layer is extracted with ethyl acetate and the combined organic layer is dried over sodium sulfate, filtered and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-ethynylphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

t-Butyl 2-(4-hydroxyphenyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decane-7-carboxylate



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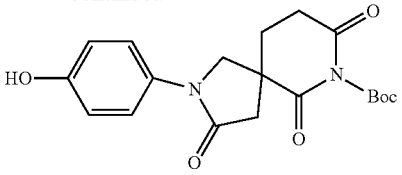
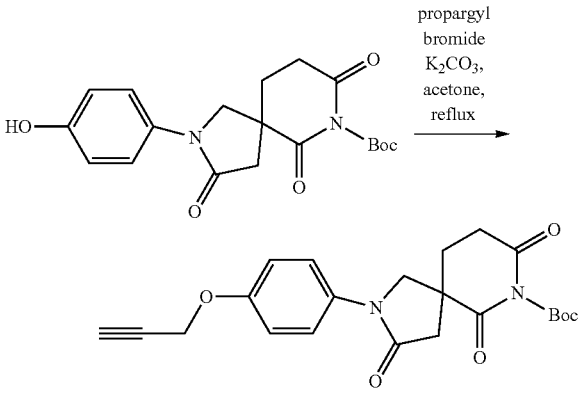


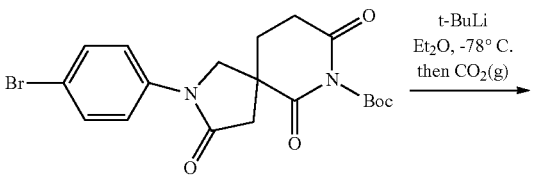
A reaction vial is charged with tris(dibenzylideneacetone) dipalladium(0) (1 mol %), 2-(di-adamantan-1-yl)phosphaneyl)-1-(2,6-diisopropylphenyl)-1H-imidazole (3 mol %), $CsOH*H_2O$ (3 equiv.). The vial is sealed, and the atmosphere is cycled between vacuum and nitrogen three times. Anhydrous THF and tert-butyl 2-(4-bromophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate are added and the reaction is mixed at ambient temperature for 20 hours. The reaction is then diluted with ethyl acetate, filtered through Celite® and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-hydroxyphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (Angew. Chem. Int. Ed. 2009, 48, 7595)

t-butyl 3,6,8-trioxo-2-(4-(prop-2-yn-1-yloxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with tert-butyl 2-(4-hydroxyphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and acetone (0.25 M). To this solution is added sequentially potassium carbonate (4 equiv.) and propargyl bromide (1.2 equiv.). The reaction is refluxed overnight, cooled to ambient temperature, filtered through a medium frit, and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 3,6,8-trioxo-2-(4-(prop-2-yn-1-yloxy)phenyl)-2,7-diazaspiro[4.5] decane-7-carboxylate. (J. Med. Chem. 2013, 56(7), 2828)

4-(7-(t-Butoxycarbonyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decan-2-yl)benzoic Acid



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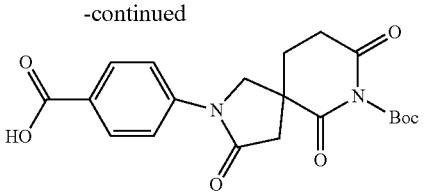
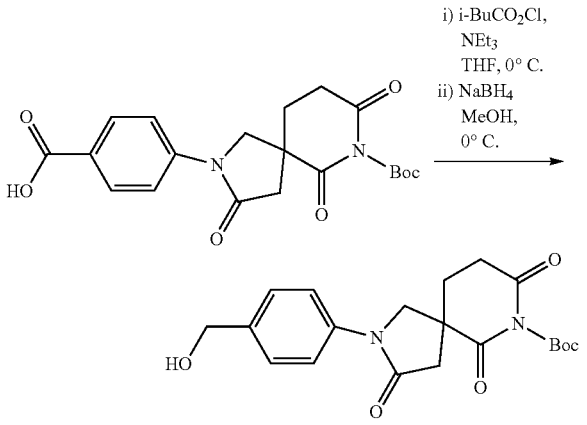


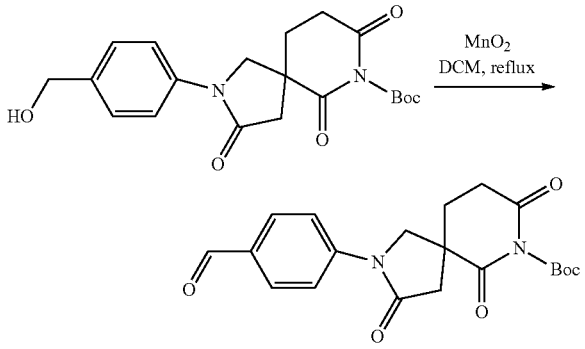
A flame-dried reaction vessel is charged with tert-butyl 2-(4-bromophenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and the atmosphere is cycled between nitrogen and vacuum three times. Ether is added and the solution is cooled to −78° C. tert-Butyllithium (2 equiv.) is added dropwise and the reaction is mixed for 15 min then carbon dioxide gas is bubbled through the solution for 15 min. The reaction is warmed to ambient temperature allowing excess carbon dioxide gas to slowly evolve from solution. The reaction is quenched with 1 M aq. NaOH solution and washed with ether (2×). The pH of the aqueous layer is adjusted to 3 and extracted with ethyl acetate (3×). The combined organic layer is dried over sodium sulfate and concentrated to dryness with toluene (3×) to provide 4-(7-(tert-butoxycarbonyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decan-2-yl)benzoic acid.

tert-Butyl-2-(4-(hydroxymethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



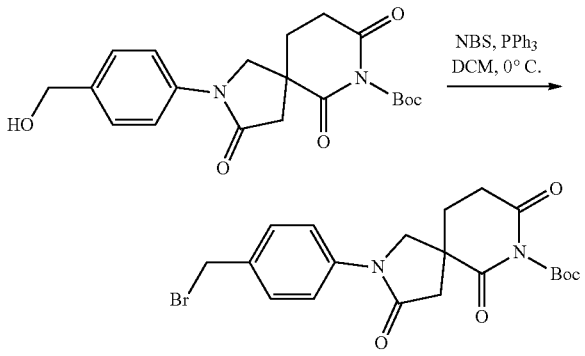
A reaction vessel was charged with 4-(7-(tert-butoxycarbonyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decan-2-yl)benzoic acid. (1 equiv.), THF and cool to 0° C. Triethylamine (1.1 equiv.) and isobutylchloroformate (1.1 equiv.) were added and the reaction mixed ambient temperature for 1 hour. The reaction is filtered through a medium frit and cooled to 0° C. To the solution of mixed anhydride is added a solution of sodium borohydride (2 equiv.) in MeOH. Upon complete reduction to the corresponding benylic alcohol, the reaction is concentrated then treated with ethyl acetate and 10% aq. HCl. The phases are separated and aqueous solution is extracted with ethyl acetate (3×). The combined organic layer is washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and concentrated. The residue is purified by silica gel chromatography to provide tert-butyl 2-(4-(hydroxymethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

tert-Butyl-2-(4-formylphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate

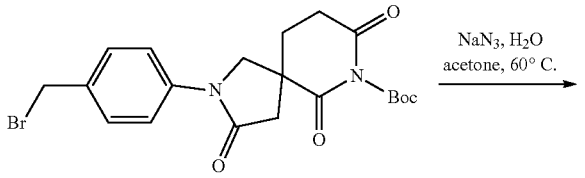


A reaction vessel is charged with tert-butyl 2-(4-(hydroxymethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and manganese dioxide (10 equiv.) and DCM. The reaction is heated at reflux overnight then cooled to ambient temperature and filtered. The filtrate is concentrated and purified by silica gel chromatography to provide tert-butyl 2-(4-formylphenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

tert-Butyl 2-(4-(bromomethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with tert-butyl 2-(4-(hydroxymethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and DCM. The solution is cooled to 0° C. and N-bromosuccinimide (1.25 equiv.) and triphenylphosphine (1.25 equiv.) are then added. The reaction is mixed for 3 hours then concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-(bromomethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (J. Med. Chem. 2015, 58(3), 1215)



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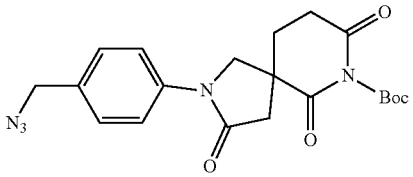
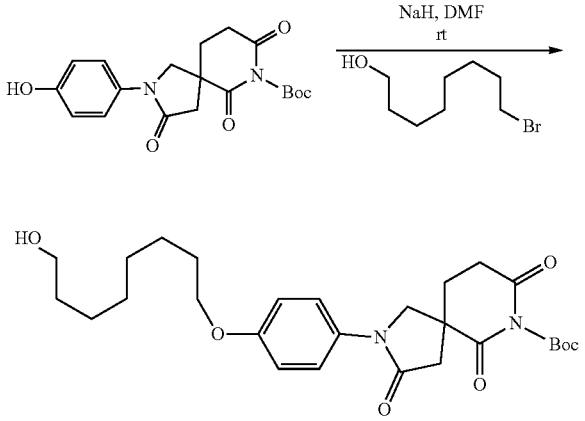


Sodium azide (3 equiv.) is added to a solution of tert-butyl 2-(4-(bromomethyl)phenyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decane-7-carboxylate (1 equiv.) in water and acetone (1:3, 0.25 M). The reaction is heated at 60° C. for 6 hours. The reaction is cooled to ambient temperature and the solvent removed by rotary evaporation. The aqueous layer is extracted with DCM (3×) and the combined organic layer is dried over sodium sulfate and filtered. The filtrate is concentrated and the crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-(azidomethyl) phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (Angew. Chem. Int. Ed. 2014, 53(38), 10155)

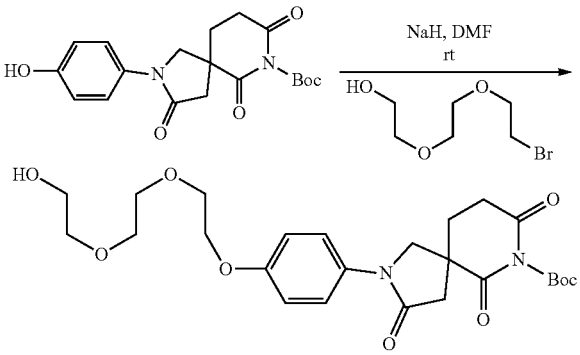
Linker Installation

t-Butyl-2-(4-((8-hydroxyoctyl)oxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



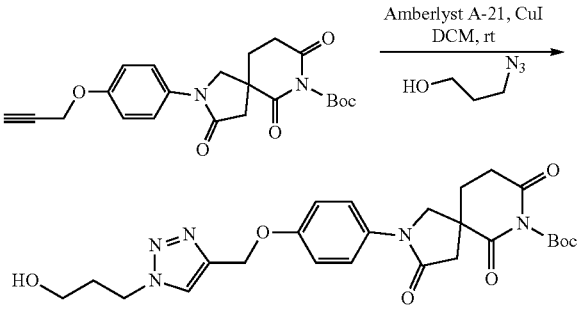
A reaction vessel is charged with tert-butyl 2-(4-hydroxyphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and DMF (0.3 M) then cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv.) is added and the reaction is warmed to ambient temperature and mixed for 1 hour. The reaction is cooled to 0° C. then 8-bromooctan-1-ol (1.1 equiv.) is added and the reaction is mixed at ambient temperature overnight. DMF is removed by rotary evaporation and the residue is deposited onto silica gel and purified by silica gel chromatography to provide tert-butyl 2-(4-((8-hydroxyoctyl)oxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

t-Butyl-2-(4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy) phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



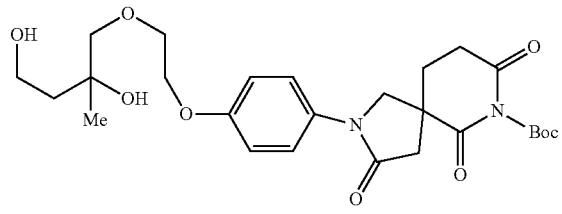
A reaction vessel is charged with tert-butyl 2-(4-hydroxyphenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and DMF (0.3 M) then cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv.) is added and the reaction is warmed to ambient temperature and mixed for 1 hour. The reaction is cooled to 0° C. then 2-(2-(2-bromoethoxy)ethoxy)ethan-1-ol (1.1 equiv.) is added and the reaction is mixed at ambient temperature overnight. DMF is removed by rotary evaporation and the residue is deposited onto silica gel and purified by silica gel chromatography to provide tert-butyl 2-(4-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)phenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

t-Butyl-2-(4-((1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decane-7-carboxylate

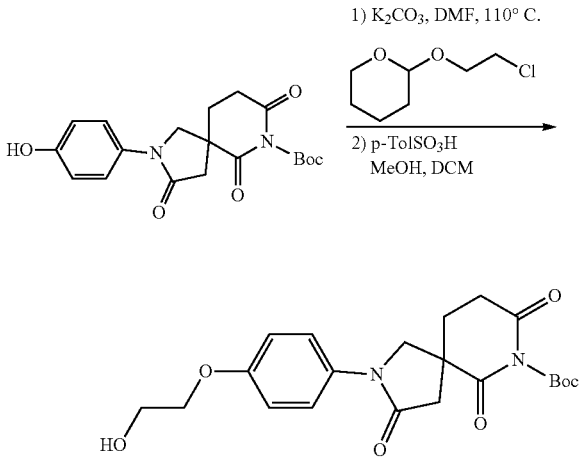


A reaction vessel is charged with the polymer supported catalyst (Amberlyst A-21, 1.23 mmol/g; CuI, 13% mol). The azide (0.5 M in DCM) is added dropwise followed by a solution of the tert-butyl 3,6,8-trioxo-2-(4-(prop-2-yn-1-yloxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (0.5 M in DCM). The suspension is mixed for 12 hours at ambient temperature. The reaction solution is filtered through a frit and the polymer cake is washed is washed with DCM (2×). The combined filtrate is concentrated and the residue purified by silica gel chromatography to provide tert-butyl 2-(4-((1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl) methoxy)phenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (*Org. Lett.* 2006, 8(8), 1689)

Linker Installation Example 1: t-Butyl-2-(4-(2-(2,4-dihydroxy-2-methylbutoxy)ethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



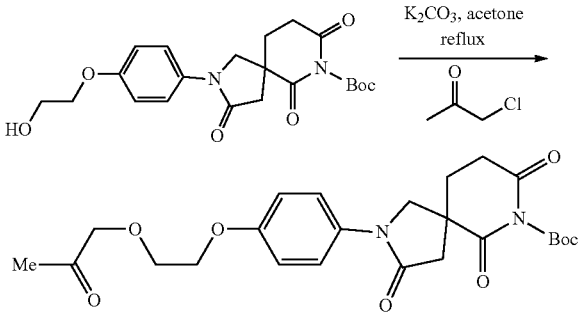
t-Butyl-2-(4-(2-hydroxyethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with tert-butyl 3,6,8-trioxo-2-(4-(prop-2-yn-1-yloxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.), potassium carbonate (2 equiv.) and DMF (0.5 M). 2-(2-Chloroethoxy)tetrahydro-2H-pyran (1.1 equiv.) is added and the reaction is heated at 110° C. for 12 hours. The reaction is then cooled to ambient temperature and concentrated. The residue is taken up in water and ethyl acetate and the layers separated. The aqueous layer is extracted with ethyl acetate (2×). The combined organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue is used directly in the following reaction.

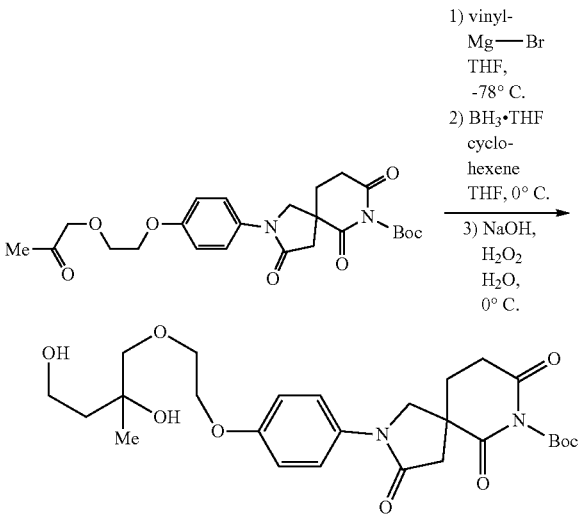
A reaction vessel is charged with crude tert-butyl 3,6,8-trioxo-2-(4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.), MeOH and DCM (1:1, 0.2 M). p-Toluenesulfonic acid (0.1 equiv.) is added and the reaction mixed at ambient temperature. Upon completion of the hydrolysis reaction, the volatiles are removed by rotary evaporation and the residue purified by silica gel chromatography to provide tert-butyl 2-(4-(2-hydroxyethoxy)phenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

tert-Butyl-3,6,8-trioxo-2-(4-(2-(2-oxopropoxy)ethoxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate



A reaction vessel is charged with tert-butyl 2-(4-(2-hydroxyethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.), potassium carbonate (1.2 equiv.) and acetone (0.1 M). Chloroacetone (1.2 equiv.) is then added and the reaction heated at reflux overnight. The reaction is cooled then concentrated and the crude residue partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×). The combined organic layers are dried over sodium sulfate, filtered and concentrated. The crude residue is purified by column chromatography to provide tert-butyl 3,6,8-trioxo-2-(4-(2-(2-oxopropoxy)ethoxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate. J. Med. Chem. 2007, 50(18), 4304)

tert-Butyl-2-(4-(2-(2,4-dihydroxy-2-methylbutoxy)ethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate

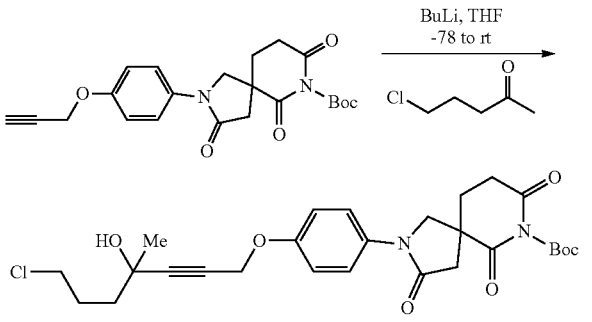


A reaction vessel is charged with tert-butyl 3,6,8-trioxo-2-(4-(2-(2-oxopropoxy)ethoxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.), and THF (0.2 M), purged with nitrogen and cooled to −78° C. Vinylmagnesium bromide (4 equiv.) is added dropwise and the reaction is

warmed to 0° C. over 1 hour. The reaction is quenched with aq. 1% HCl solution and extracted with ethyl acetate (3×). The combined organic layer is washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-(2-((2-hydroxy-2-methylbut-3-en-1-yl)oxy)ethoxy) phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

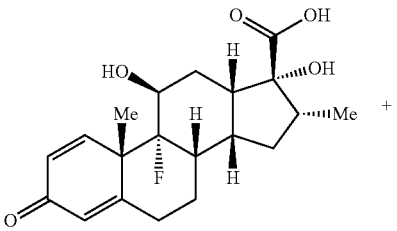
Cyclohexene (4.2 equiv.) was added to a solution of BH3-THF (1 M in THF, 2 equiv.) at 0° C. under argon. After stirring for 1 hour at 0° C., a solution of tert-butyl 2-(4-(2-((2-hydroxy-2-methylbut-3-en-1-yl)oxy)ethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) in THF (0.15 M) was added to the mixture at 0° C. After stirring for 2 hours at 0° C., 3N NaOH (6 equiv.) and 30% H_2O_2 (33% volume of aq. NaOH solution addition) was added to the mixture. This solution is allowed to mix at ambient temperature for 30 min. The reaction is quenched with saturated aqueous NH_4C_1 (8 volumes) at 0° C., and the resulting mixture is extracted with ethyl acetate (3×). The combined extracts are washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-(2-(2,4-dihydroxy-2-methylbutoxy) ethoxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate. (*Org. Lett.* 2012, 14(24), 6374)

tert-Butyl-2-(4-((7-chloro-4-hydroxy-4-methylhept-2-yn-1-yl)oxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro [4.5]decane-7-carboxylate

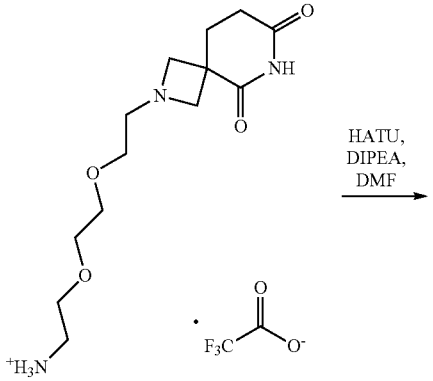


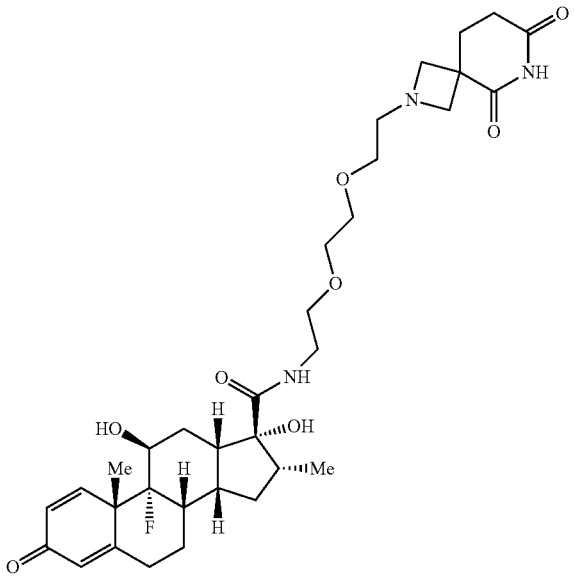
A reaction vessel is charged with tert-butyl 3,6,8-trioxo-2-(4-(prop-2-yn-1-yloxy)phenyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (1 equiv.) and the atmosphere cycled between nitrogen and vacuum three times. Anhydrous THF (0.1 M) is added and the reaction cooled to −78° C. Butyllithium (1.05 equiv.) is added and the reaction is mixed for 15 min. 5-Chloro-2-pentanone (1.1 equiv.) in THF (5 volumes) is then added and the reaction is warmed to ambient temperature and quenched with sat. aq. ammonium chloride solution. Ethyl acetate is added and the phases are separated. The aqueous layer is extracted with ethyl acetate (2×). The combined organic layers are washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue is purified by silica gel chromatography to provide tert-butyl 2-(4-((7-chloro-4-hydroxy-4-methylhept-2-yn-1-yl)oxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate.

Final Compound Examples



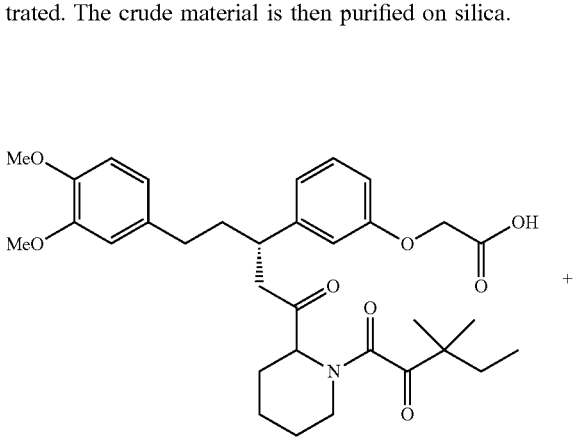
Glucocorticoid receptor targeting ligand
Dex-acid
derived from dexamethazone



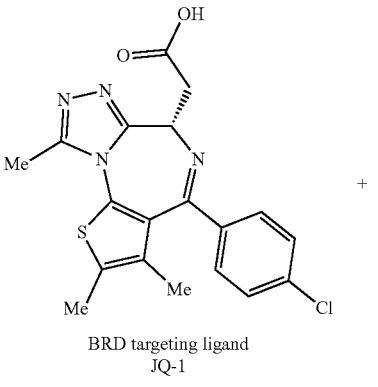


2-(2-(2-(5,7-Dioxo-2,6-diazaspiro[3.5]nonan-2-yl) ethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate (1 equiv.) is dissolved in DMF and added to a solution of Dex-acid (1 equiv.), DIPEA (3 equiv.). HATU (1 equiv.) is then added and the mixture is stirred for 24 hours. The mixture is then diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, water, and then brine.

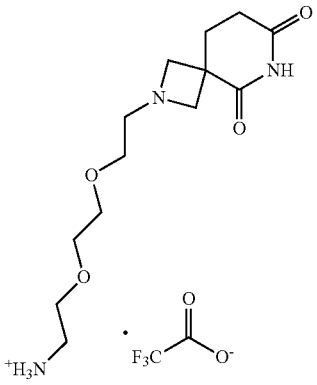
The organic layer is dried over sodium sulfate and concentrated. The crude material is then purified on silica.



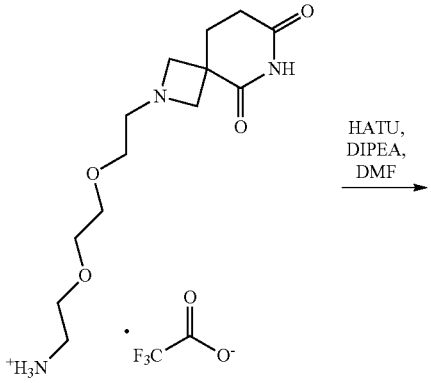
FKBP targeting ligand
AP1479



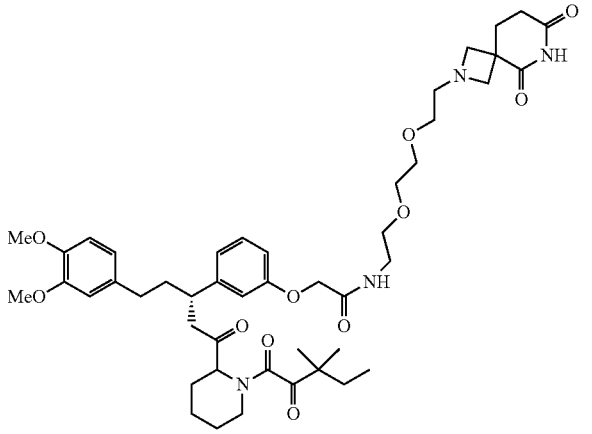
BRD targeting ligand
JQ-1

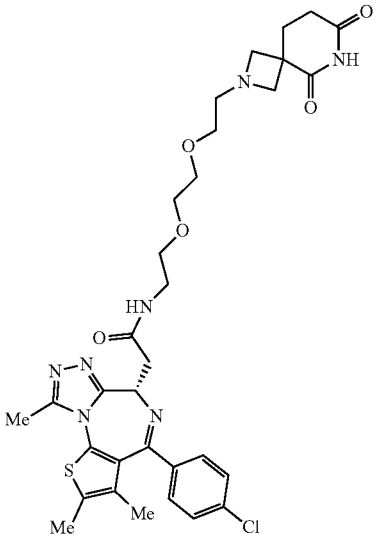


HATU,
DIPEA,
DMF



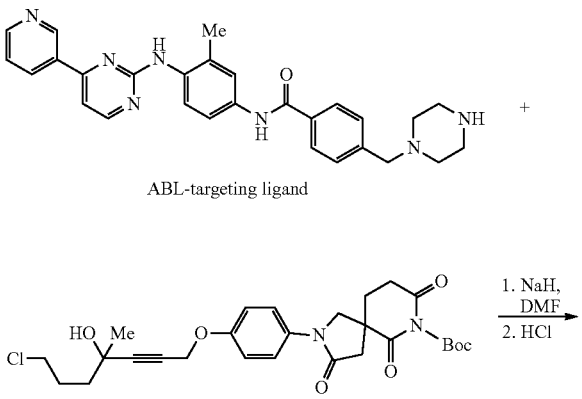
HATU,
DIPEA,
DMF



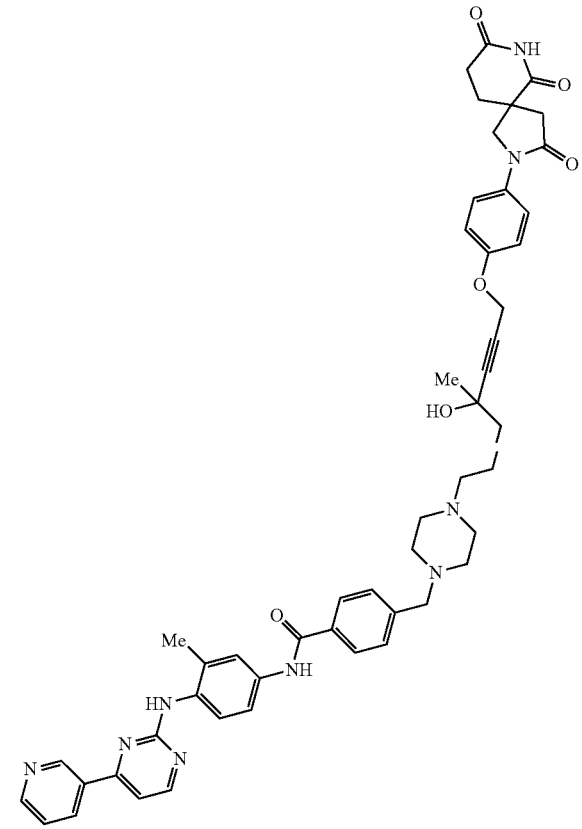


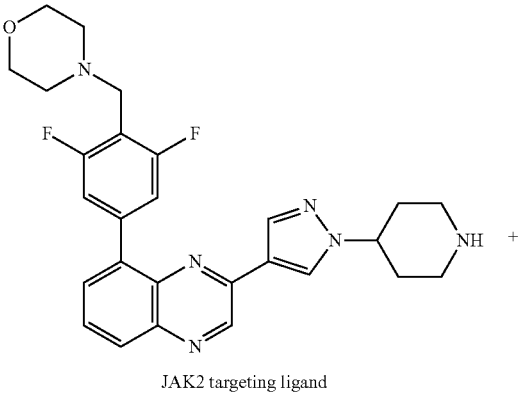
2-(2-(2-(5,7-dioxo-2,6-diazaspiro[3.5]nonan-2-yl) ethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate (1 equiv.) is dissolved in DMF and added to a solution of AP1479 (1 equiv.), DIPEA (3 equiv.). HATU (1 equiv.) is then added and the mixture is stirred for 24 hours. The mixture is then diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, water, and then brine. The organic layer is dried over sodium sulfate and concentrated. The crude material is then purified on silica.

2-(2-(2-(5,7-Dioxo-2,6-diazaspiro[3.5]nonan-2-yl) ethoxy)ethoxy)ethan-1-aminium 2,2,2-trifluoroacetate (1 equiv.) is dissolved in DMF and added to a solution of JQ-1 (1 equiv.), DIPEA (3 equiv.). HATU (1 equiv.) is then added and the mixture is stirred for 24 hours. The mixture is then diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, water, and then brine. The organic layer is dried over sodium sulfate and concentrated. The crude mater is then purified on silica.

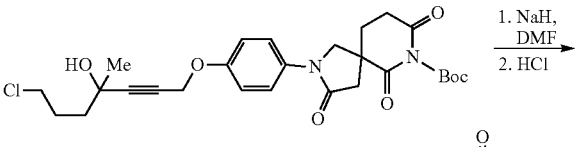


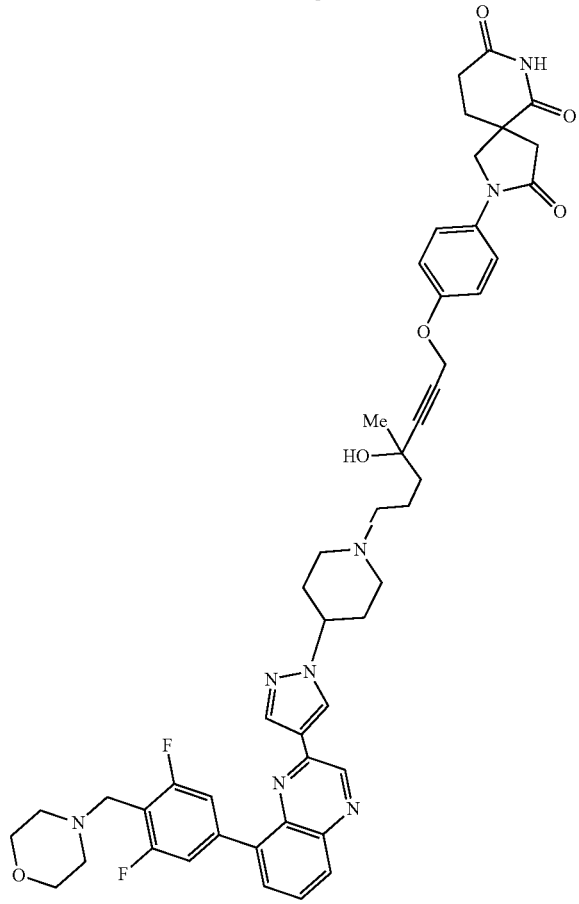
ABL-targeting ligand





JAK2 targeting ligand





A reaction vessel is charged with N-(3-methyl-4-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-(piperazin-1-ylmethyl)benzamide (1 equiv.) and DMF (0.3 M) then cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv.) is added and the reaction is warmed to ambient temperature and mixed for 1 hour. The reaction is cooled to 0° C. then tert-butyl 2-(4-((7-chloro-4-hydroxy-4-methylhept-2-yn-1-yl)oxy)phenyl)-3,6, 8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1.1 equiv.) is added and the reaction is mixed at ambient temperature overnight. DMF is removed by rotary evaporation. The crude material is then dissolved in dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude product is purified on silica.

A reaction vessel is charged with 4-(2,6-difluoro-4-(3-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinoxalin-5-yl)benzyl) morpholine (1 equiv.) and DMF (0.3 M) then cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv.) is added and the reaction is warmed to ambient temperature and mixed for 1 hour. The reaction is cooled to 0° C. then tert-butyl 2-(4-((7-chloro-4-hydroxy-4-methylhept-2-yn-1-yl)oxy)phenyl)-3,6,8-trioxo-2,7-diazaspiro[4.5]decane-7-carboxylate (1.1 equiv.) is added and the reaction is mixed at ambient temperature overnight. DMF is removed by rotary evaporation. The crude material is then dissolved in

dioxane. HCl (4N in dioxane) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude product is purified on silica.

ADDITIONAL EXAMPLES

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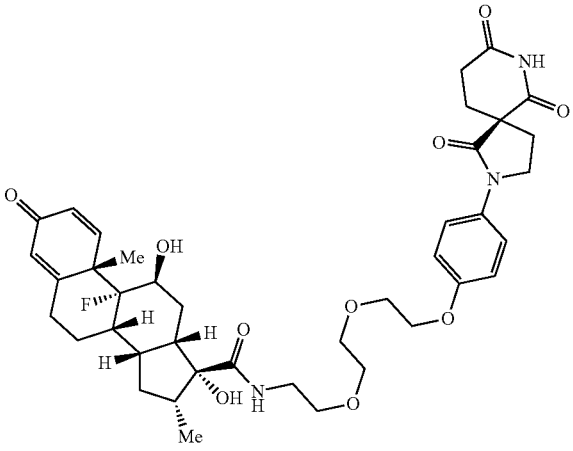

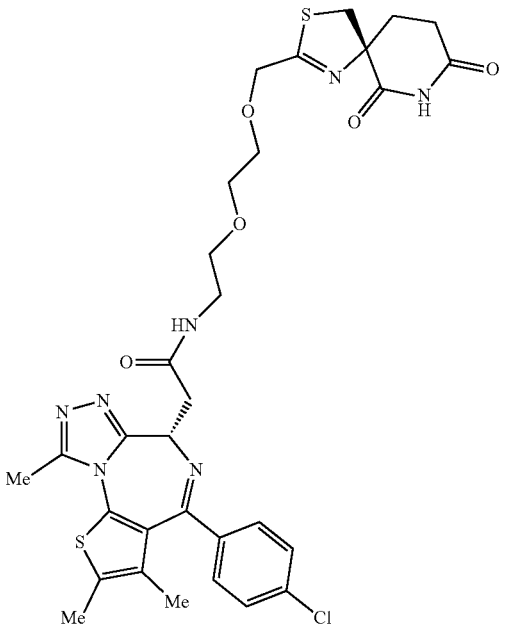

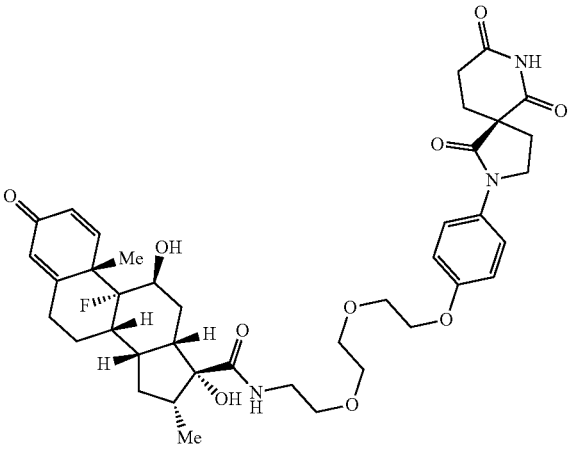

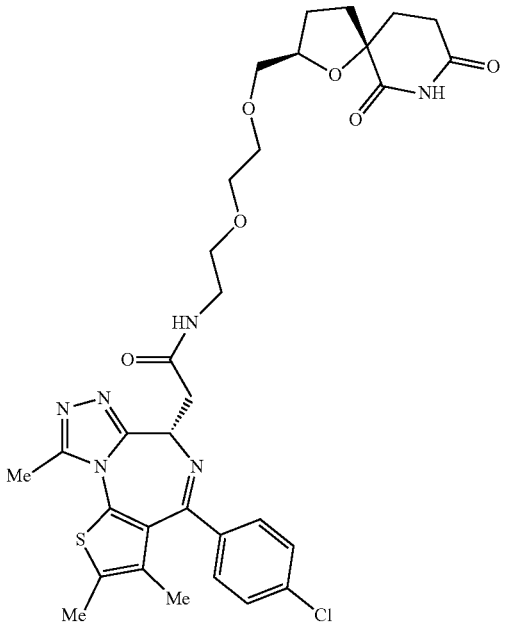

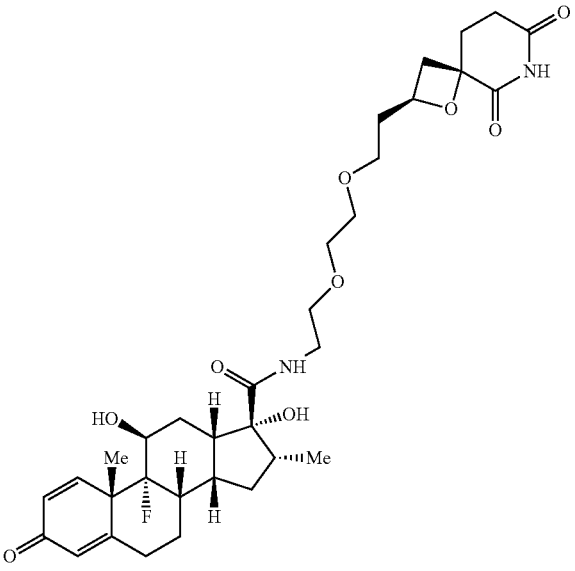

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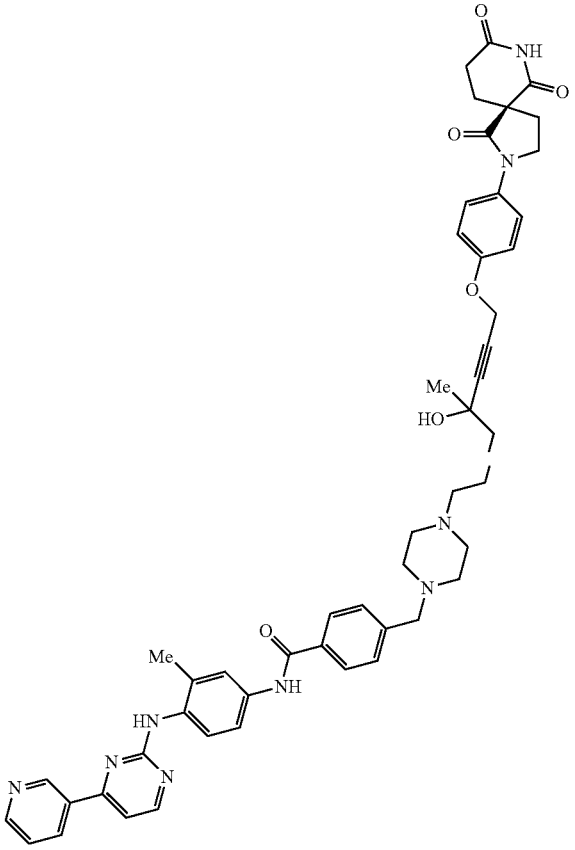

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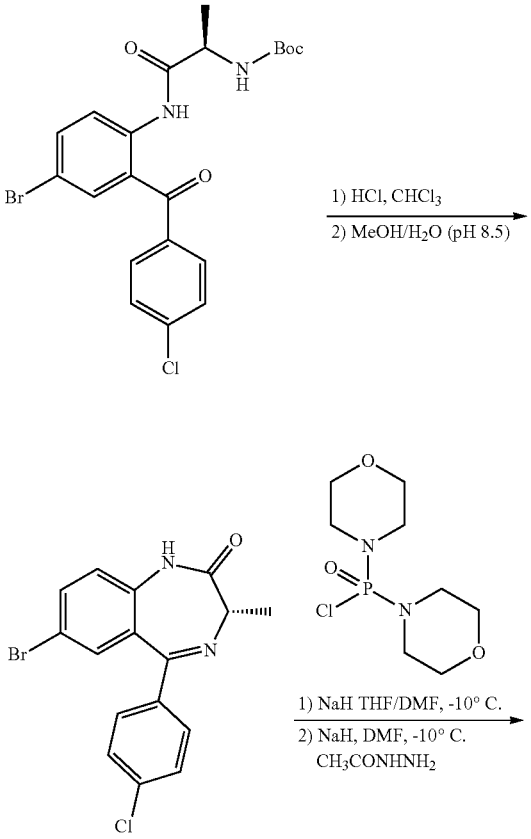
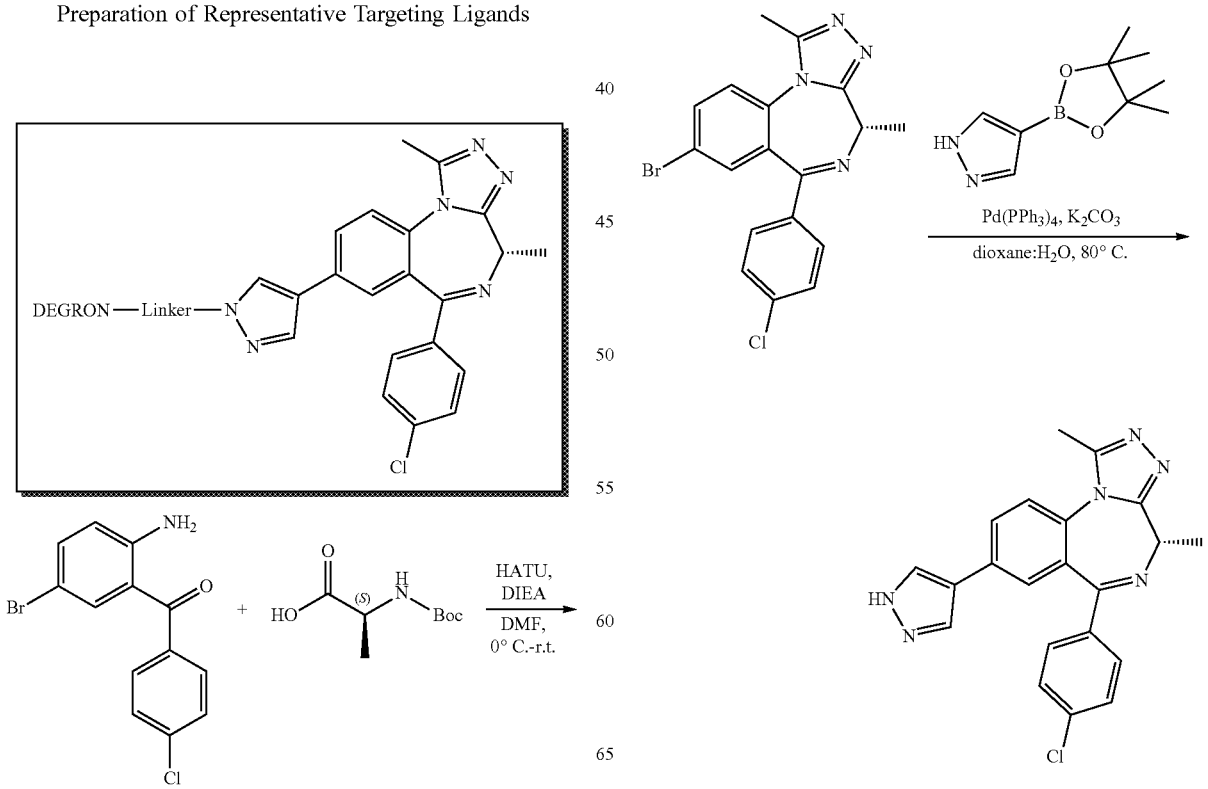
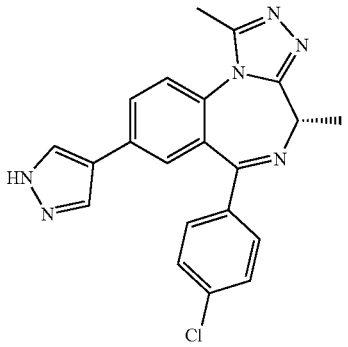


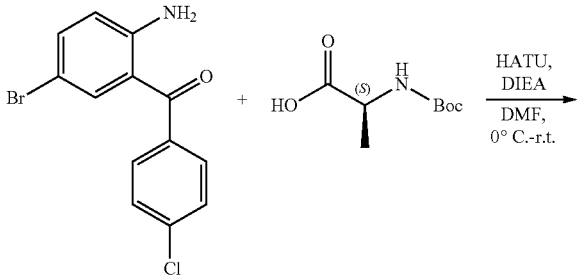
Preparation of Representative Targeting Ligands

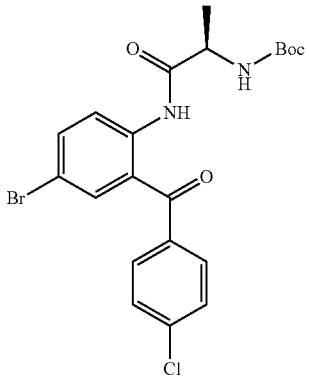


(S)-6-(4-Chlorophenyl)-1,4-dimethyl-8-(1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine



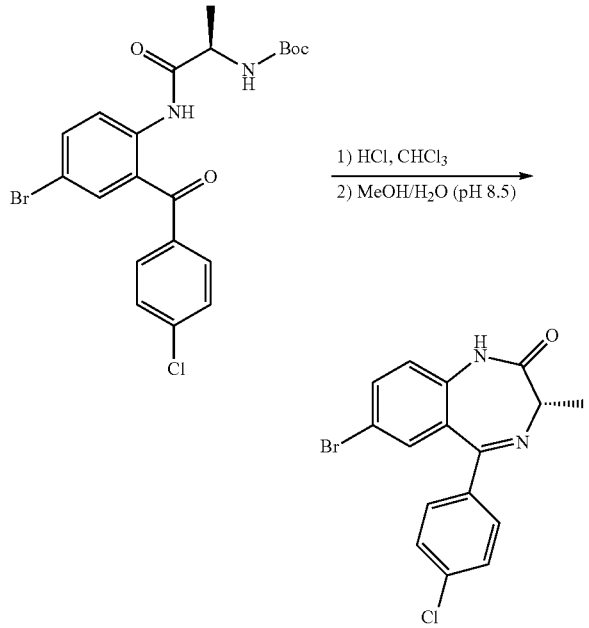
Tert-Butyl (R)-(1-((4-bromo-2-(4-chlorobenzoyl)phenyl)amino)-1-oxopropan-2-yl)carbamate





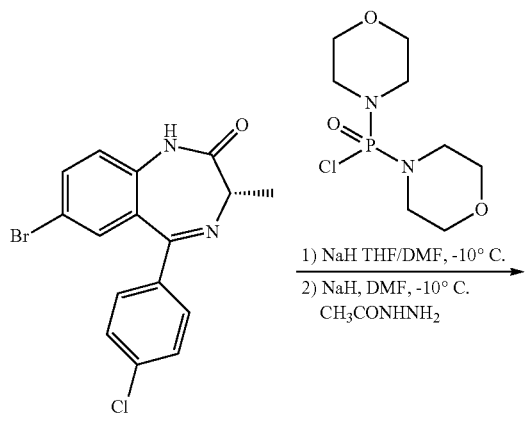
(2-Amino-5-bromophenyl)(4-chlorophenyl)methanone (1.0 equiv.) and Boc-(L)-Ala (1.0 equiv.) is suspended in DMF and cooled to 0° C. DIEA (2.0 equiv.) is added followed by HATU (1.1 equiv.) and the reaction is stirred at reduced temperature for 30 minutes and then warmed to room temperature. When the reaction is judged to be complete it is quenched with aq. ammonium chloride and extracted with ethyl acetate. The combined organic layers are dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide tert-butyl (R)-(1-((4-bromo-2-(4-chlorobenzoyl)phenyl)amino)-1-oxopropan-2-yl)carbamate.

(S)-7-Bromo-5-(4-chlorophenyl)-3-methyl-1,3-dihydro-2H-benzo[e][1,4] diazepin-2-one



To a stirred solution of boc protected amine in $CHCl_3$ at r.t., is added hydrogen chloride gas slowly. After 20 minutes the addition is stopped and the reaction is stirred at r.t. until deprotection is complete. The reaction mixture is then washed with saturated bicarbonate solution (2×) and water (2×). The organic layer is concentrated under reduced pressure. The residue is dissolved in 2:1 methanol:water and the pH is adjusted to 8.5 by the addition of 1N aqueous NaOH. The reaction is then stirred at r.t. until the cyclization is complete. MeOH is then removed under reduced pressure and the solution is extracted with DCM (3×). The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide (S)-7-bromo-5-(4-chlorophenyl)-3-methyl-1,3-dihydro-2H-benzo[e][1,4]diazepin-2-one (US 2010 0261711.).

(S)-8-Bromo-6-(4-chlorophenyl)-1,4-dimethyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine



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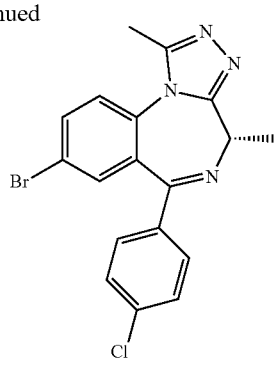
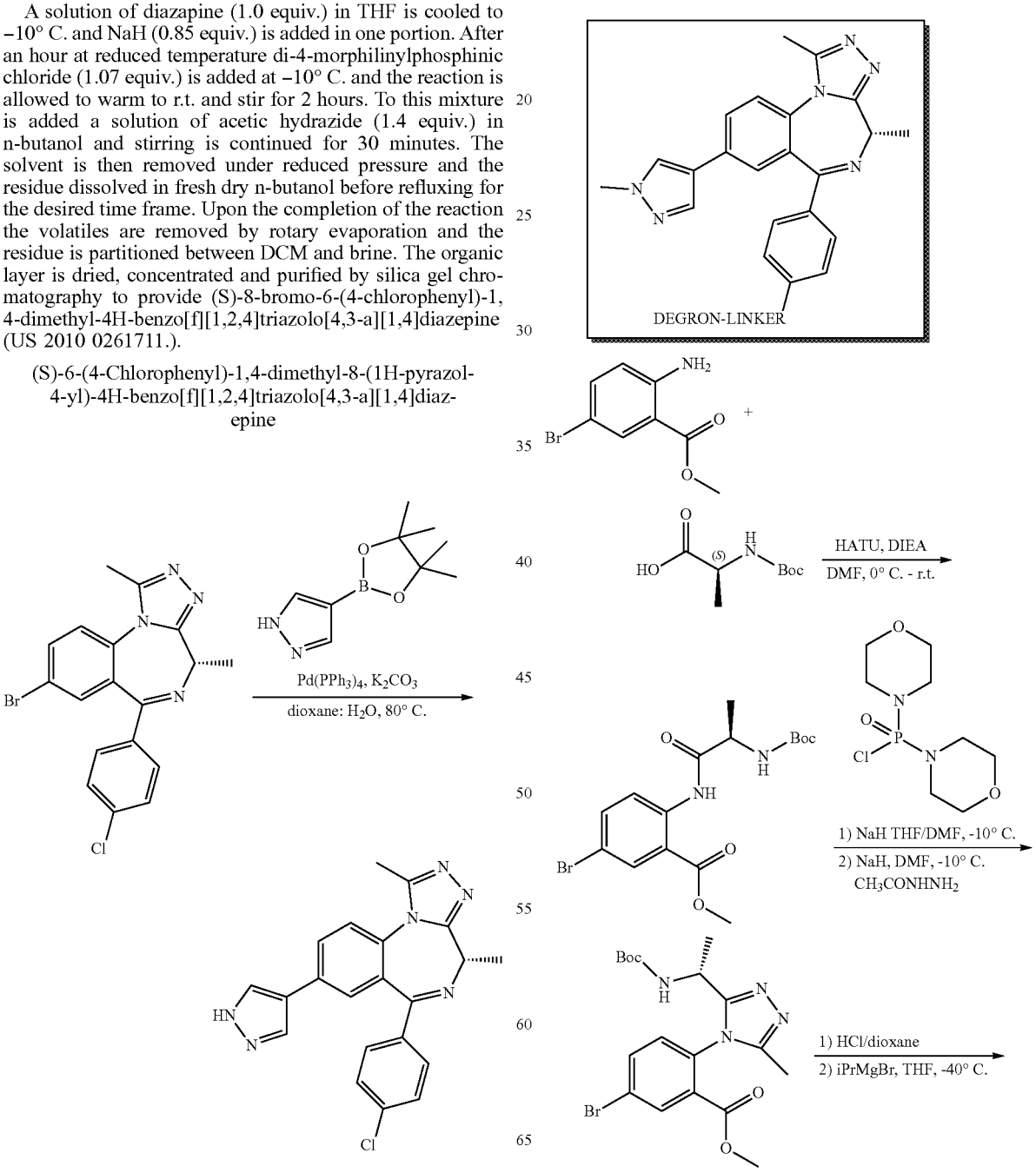


A solution of diazapine (1.0 equiv.) in THF is cooled to −10° C. and NaH (0.85 equiv.) is added in one portion. After an hour at reduced temperature di-4-morphilinylphosphinic chloride (1.07 equiv.) is added at −10° C. and the reaction is allowed to warm to r.t. and stir for 2 hours. To this mixture is added a solution of acetic hydrazide (1.4 equiv.) in n-butanol and stirring is continued for 30 minutes. The solvent is then removed under reduced pressure and the residue dissolved in fresh dry n-butanol before refluxing for the desired time frame. Upon the completion of the reaction the volatiles are removed by rotary evaporation and the residue is partitioned between DCM and brine. The organic layer is dried, concentrated and purified by silica gel chromatography to provide (S)-8-bromo-6-(4-chlorophenyl)-1,4-dimethyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine (US 2010 0261711.).

(S)-6-(4-Chlorophenyl)-1,4-dimethyl-8-(1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine

To a vial containing (S)-8-bromo-6-(4-chlorophenyl)-1,4-dimethyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine (1 equiv.) is added Pd(PPh3)4 (20 mol %), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 equiv.), and potassium carbonate (2.5 equiv.). The vial is then evacuated and purged under N2. To the vial is added dioxane:water (2:1). The contents were once again evacuated and purged under N2 and the reaction mixture was heated to 80° C. until the SM is converted. The mixture is then cooled to room temperature and filtered over a pad of Celite®. The filter pad is rinsed with EtOAc (3×) and the filtrate is concentrate. The crude material is purified by flash chromatography (WO 2015156601).



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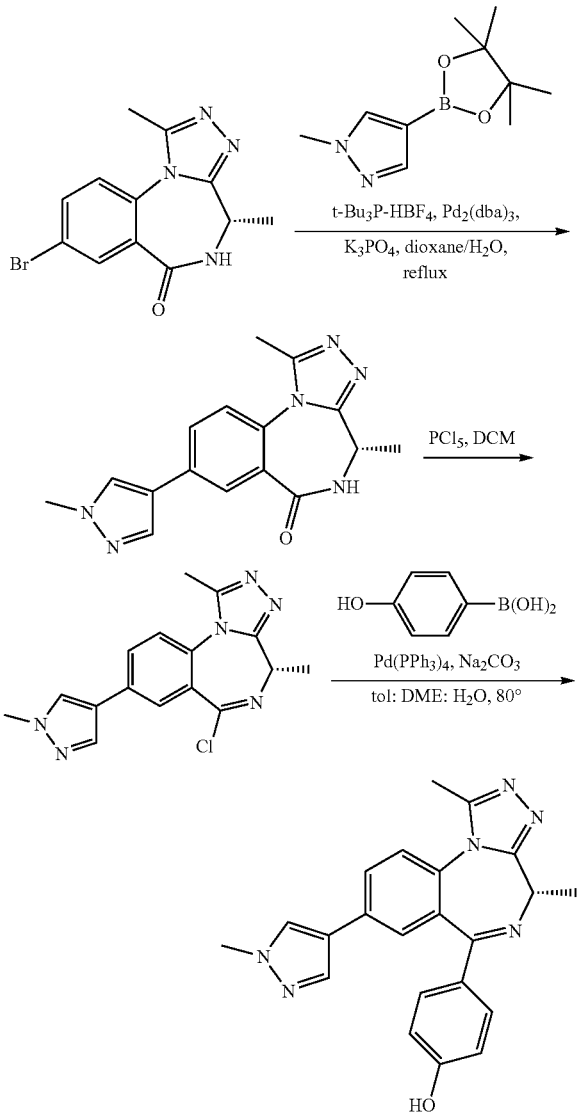
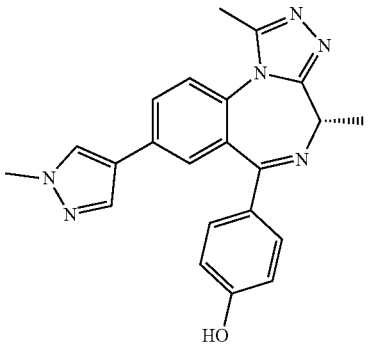
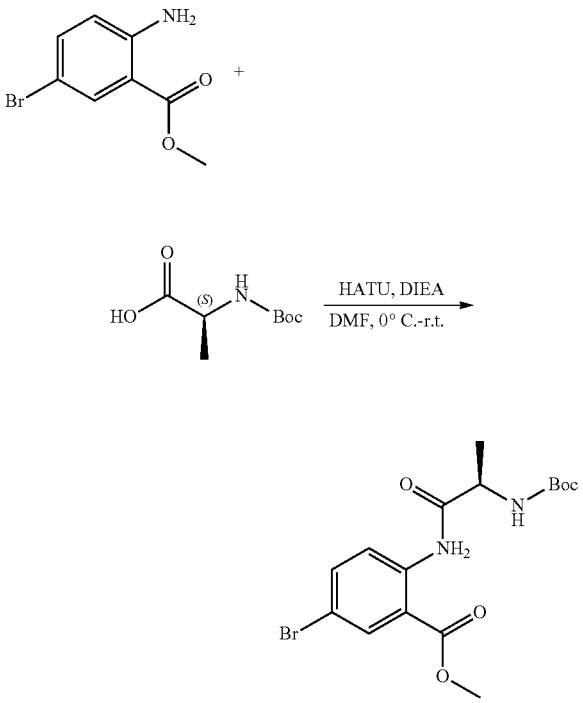


(S)-4-(1,4-Dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl) phenol

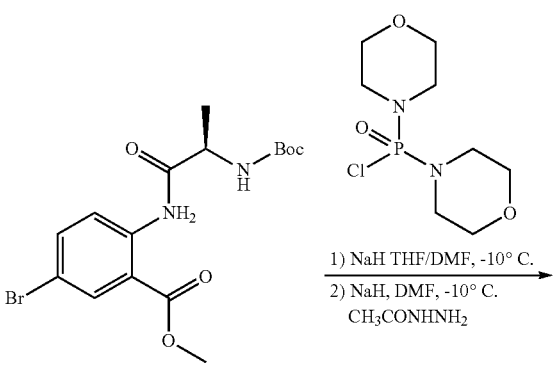


Methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl) amino)propanamido)benzoate



Methyl 2-amino-5-bromobenzoate (1.0 equiv.) and Boc-(L)-Ala (1.0 equiv.) is suspended in DMF and cooled to 0° C. DIEA (2.0 equiv.) is added followed by HATU (1.1 equiv.) and the reaction is stirred at reduced temperature for 30 minutes and then warmed to room temperature. When the reaction is judged to be complete it is quenched with aq. ammonium chloride and extracted with ethyl acetate. The combined organic layers are dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl) amino)propanamido)benzoate.

Methyl 5-bromo-2-(3-((R)-1-((tert-butoxycarbonyl) amino)ethyl)-5-methyl-4H-1,2,4-triazol-4-yl)benzoate



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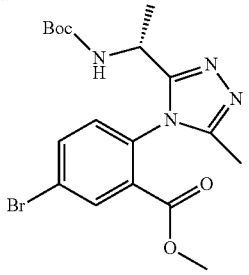
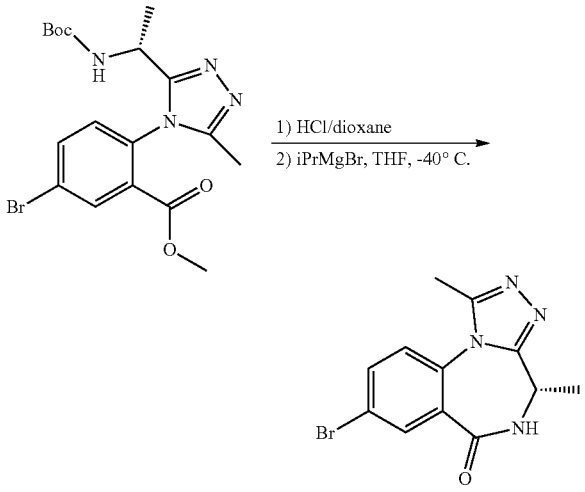


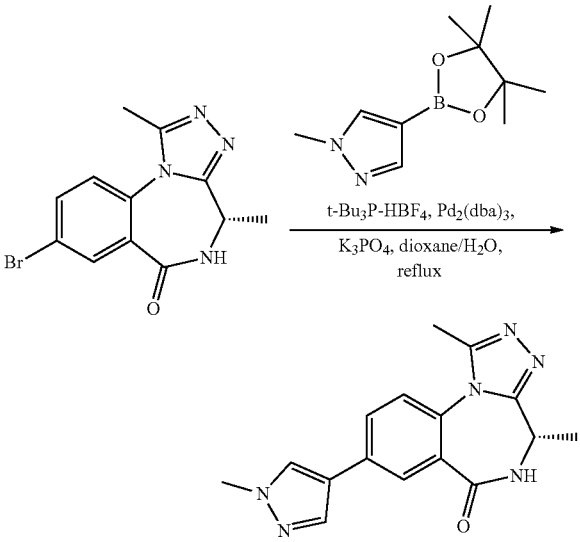
Methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl)amino) propanamido)benzoate A solution of methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl)amino)propanamido)benzoate (1.0 equiv.) in THF is cooled to −10° C. and NaH (0.85 equiv.) is added in one portion. After an hour at reduced temperature di-4-morphilinylphosphinic chloride (1.07 equiv.) is added at −10° C. and the reaction is allowed to warm to r.t. and stir for 2 hours. To this mixture is added a solution of acetic hydrazide (1.4 equiv.) in n-butanol and stirring is continued for 30 minutes. The solvent is then removed under reduced pressure and the residue dissolved in fresh dry n-butanol before refluxing for the desired time frame. Upon the completion of the reaction the volatiles are removed by rotary evaporation and the residue is partitioned between DCM and brine. The organic layer is dried, concentrated and purified by silica gel chromatography to provide methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl) amino)propanamido)benzoate (BMCL 2015, 25, 1842-48).

(S)-8-Bromo-1,4-dimethyl-4,5-dihydro-6H-benzo[f] [1,2,4]triazolo[4,3-a][1,4]diazepin-6-one



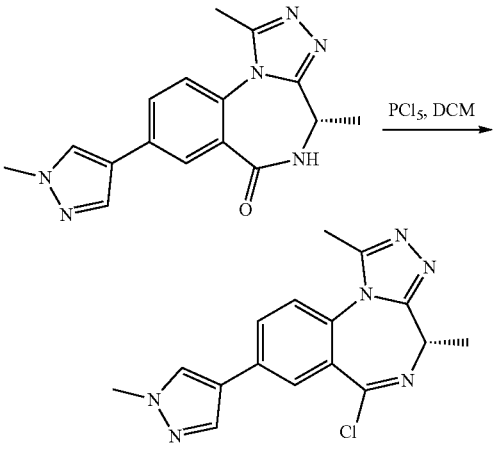
Methyl (R)-5-bromo-2-(2-((tert-butoxycarbonyl)amino) propanamido)benzoate is brought up in DCM and cooled to 0° C. 4M HCl in dioxane is added and the reaction is warmed to r.t. When deprotection is complete the reaction is concentrated and then azeotroped from toluene (2×). The crude amine salt is then dissolved in THF and cooled to −40° C. at which time iPrMgBr solution is added dropwise (2.0 equiv.) and the reaction is stirred at reduced temp until complete conversion (BMCL 2015, 25, 1842-48).

(S)-1,4-Dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4,5-dihydro-6H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-one



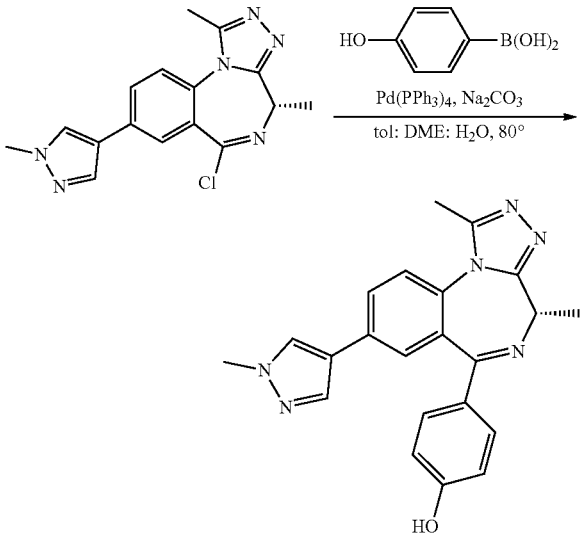
To a vial containing (S)-8-bromo-1,4-dimethyl-4,5-dihydro-6H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-one (1 equiv.) is added Pd2 (dba) 3 (10 mol %), tri-tert-butylphosphonium tetrafluoroborate (20 mol %), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 equiv.), and potassium phosphate tribasic, monohydrate (2.5 equiv.). The vial is then evacuated and purged under N2. To the vial is added 20:1 ratio by volume of dioxane:water. The contents were once again evacuated and purged under N2 (g) and the reaction mixture was heated to 100° C. until the SM is converted. The mixture is then cooled to room temperature and filtered over a pad of Celite®. The filter pad is rinsed with EtOAc (3×) and the filtrate is concentrate. The crude material is purified by flash chromatography.

(S)-6-Chloro-1,4-dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine

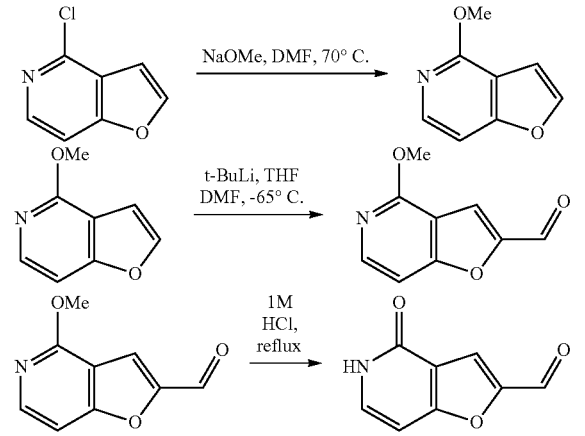


(S)-1,4-Dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4,5-dihydro-6H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-one (1.0 equiv.) is dissolved in DCM and PCI5 (1.7 equiv.) is added in one-portion. After conversion of SM 2M sodium carbonate is added. The biphasic mixture is subsequently extracted with EtOAc (4×). The combined organic layers were dried over sodium sulfate and concentrated to dryness. The resultant residue is purified by flash chromatography.

(S)-4-(1,4-Dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl) phenol



To a vial containing ((S)-6-chloro-1,4-dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepine (1 equiv.) is added $Pd(PPh_3)_4$ (20 mol %), 4-hydroxy-Phenyl boronic acid (1.5 equiv.), and sodium carbonate (2.5 equiv.). The vial is then evacuated and purged under N2. To the vial is added tol:DME:water (1:1:5). The contents were once again evacuated and purged under N2 and the reaction mixture was heated to 80° C. until the SM is converted. The mixture is then cooled to room temperature and filtered over a pad of Celite®. The filter pad is rinsed with EtOAc (3×) and the filtrate is concentrate. The crude material is purified by flash chromatography.



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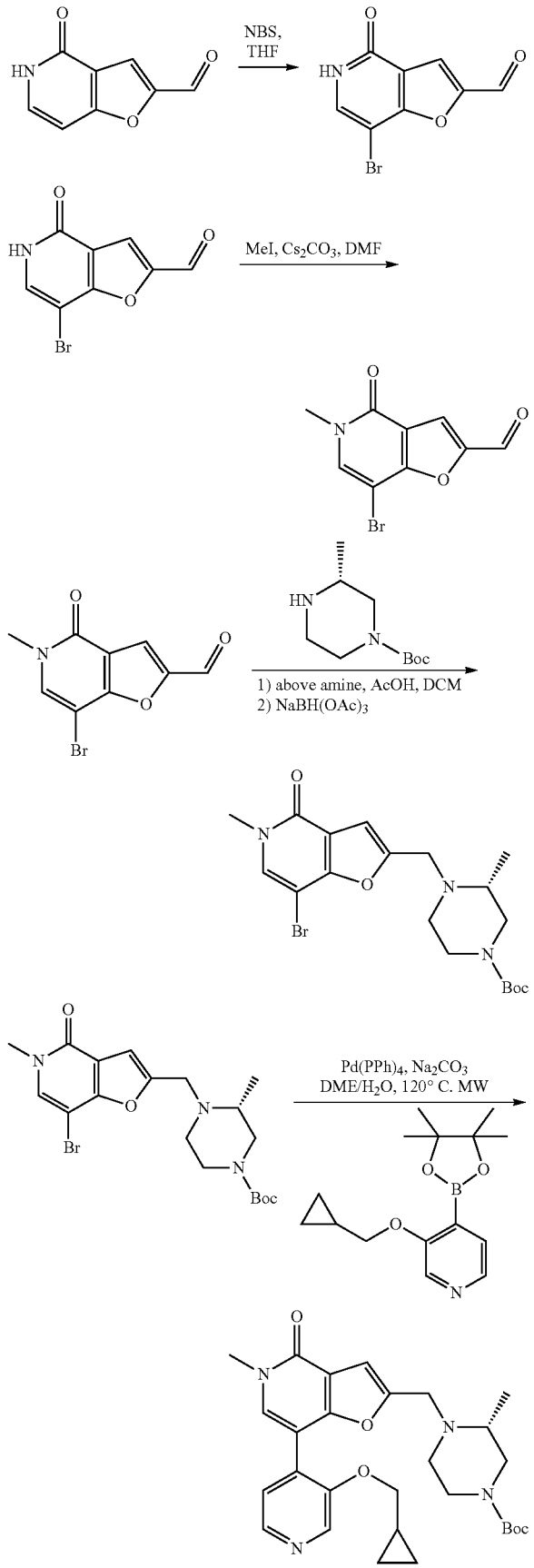

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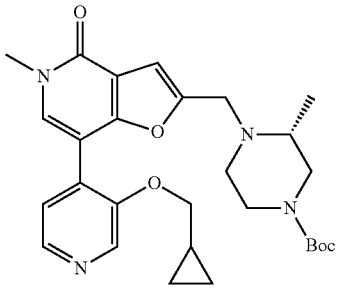
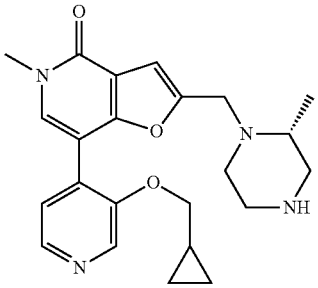
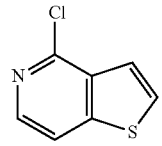
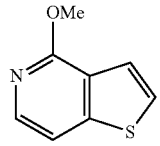


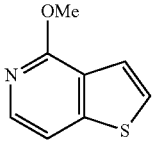
4M HCl/dioxane



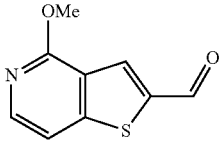


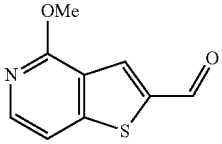
NaOMe, DMF, 70° C.



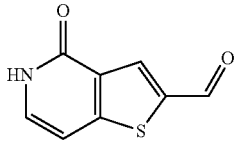


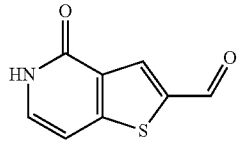
t-BuLi, THF
DMF, -65° C.



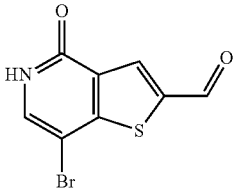


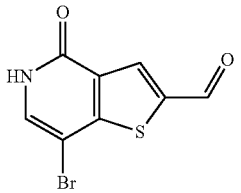
1M
HCl,
reflux



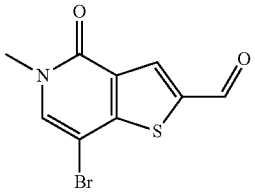


NBS,
THF





MeI, Cs_2CO_3, DMF



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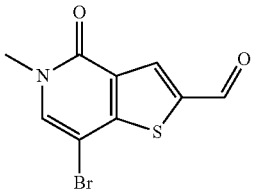
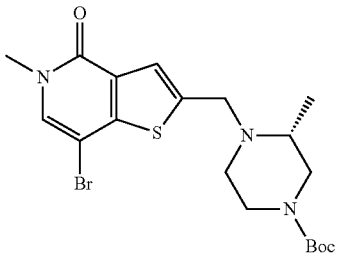
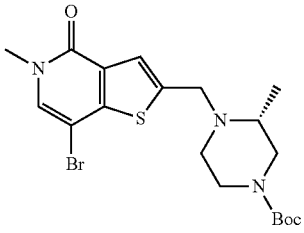
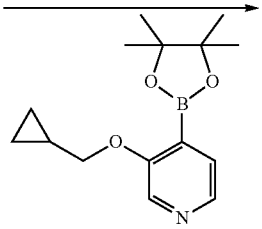


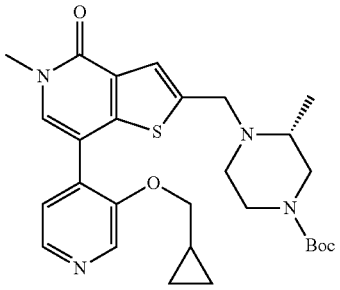
1) above amine, AcOH, DCM
2) $NaBH(OAc)_3$

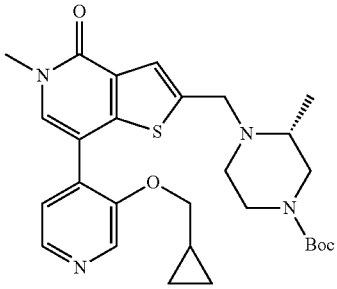




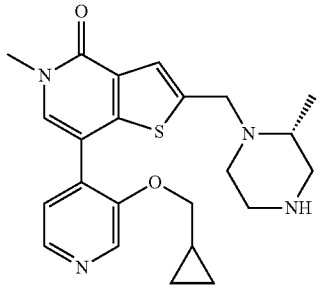
$Pd(PPh)_4$, Na_2CO_3
DME/H_2O, 120° C. MW





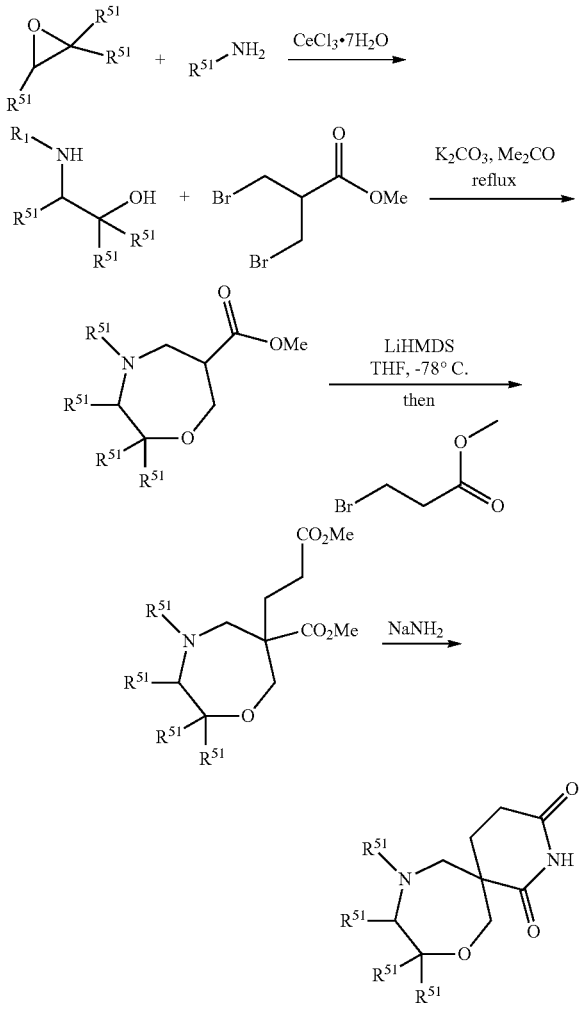


4M HCl/dioxane



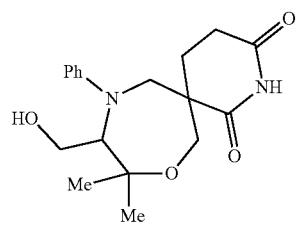
VIII. Additional Syntheses of Representative Compounds

General scheme

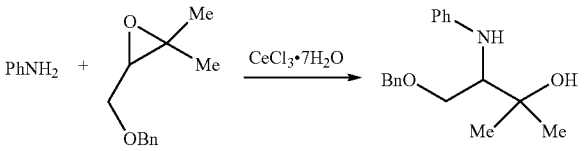


R^{51} is independently selected from H, Alk, Ar, HetAr

Representative Synthesis 1: 10-(Hydroxymethyl)-9, 9-dimethyl-11-phenyl-8-oxa-2,11-diazaspiro[5.6] dodecane-1,3-dione

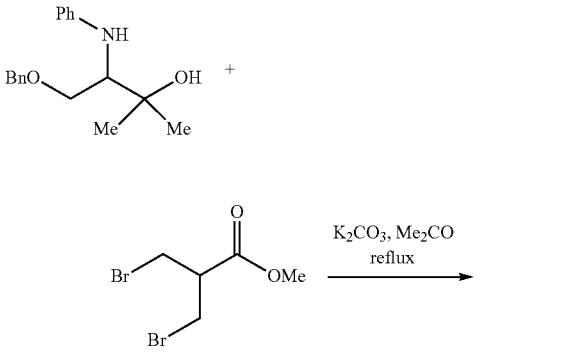


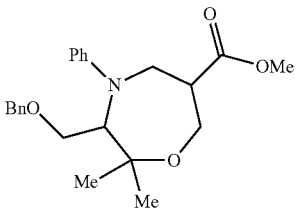
4-(Benzyloxy)-2-methyl-3-(phenylamino)butan-2-ol



To a stirred mixture of epoxide (1 equiv.) in glycerine is added the amine (1 equiv.) and $CeCl_3*7H_2$ (0.1 equiv.) at room temperature. The reaction mixture is stirred until the starting material is consumed as judged by TLC or LCMS analysis. The reaction mixture is then extracted with ethyl acetate (3×) and the combined organic layers are washed with water (2×) and brine before drying over sodium sulfate and concentrating under reduced pressure. The crude product is purified on silica to afford the ethanolamine derivative. *Synthesis,* 2011, 3, 485-489.

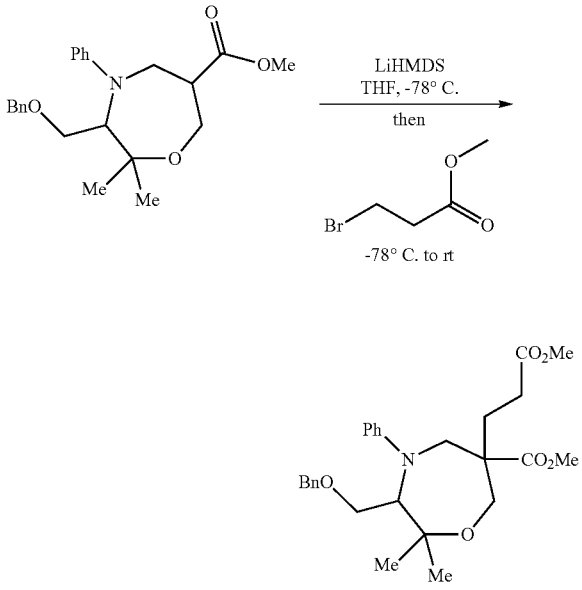
Methyl 3-((benzyloxy)methyl)-2,2-dimethyl-4-phenyl-1,4-oxazepane-6-carboxylate





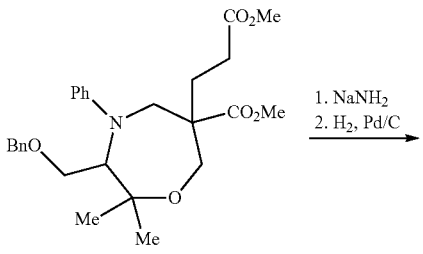
A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), ethanolamine derivative (1 equiv.) and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired cyclized adduct see for example PCT Int. Appl., 2010139481.

Methyl 3-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-4-phenyl-1,4-oxazepane-6-carboxylate



Methyl 3-((benzyloxy)methyl)-2,2-dimethyl-4-phenyl-1,4-oxazepane-6-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) is then added dropwise. The mixture is allowed to stir for 30 minutes and then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 3-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-4-phenyl-1,4-oxazepane-6-carboxylate.

10-(Hydroxymethyl)-9,9-dimethyl-11-phenyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione



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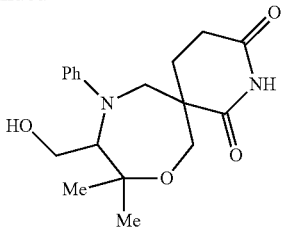
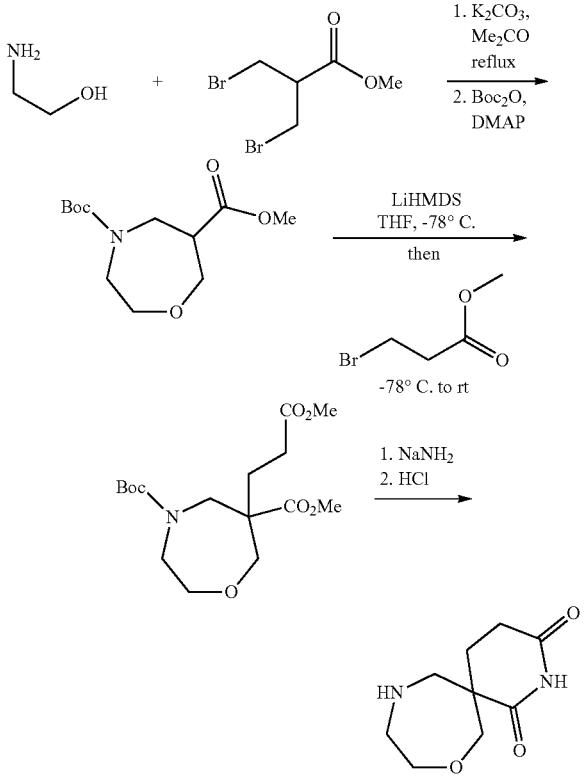
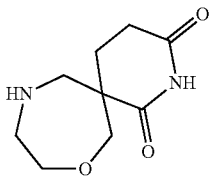


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 3-((benzyloxy)methyl)-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-4-phenyl-1,4-oxazepane-6-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography. The benzyl protected alcohol is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 10-(hydroxymethyl)-9,9-dimethyl-11-phenyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione. *Synthesis,* 1985, (4), 402-403.

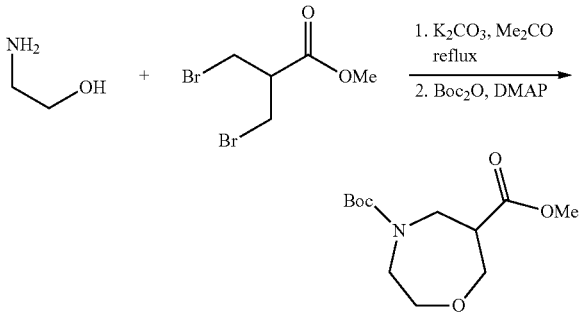
General scheme



Representative Synthesis 2: 8-Oxa-2,11-diazaspiro [5.6]dodecane-1,3-dione

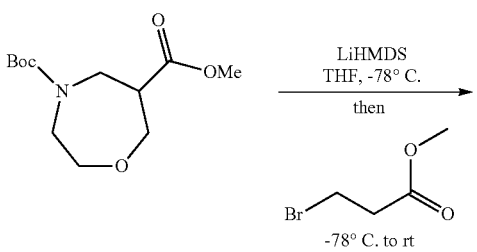


4-(tert-Butyl) 6-methyl 1,4-oxazepane-4,6-dicarboxylate



A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), ethanolamine (1 equiv.) and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired cyclized adduct. The free cyclized adduct is then dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. PCT Int. Appl., 2010/13/9481.

4-(tert-Butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-1,4-oxazepane-4,6-dicarboxylate



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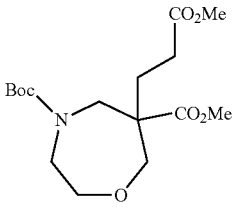
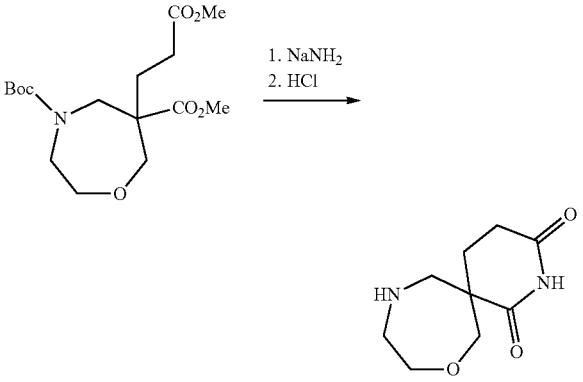


4-(tert-Butyl) 6-methyl 1,4-oxazepane-4,6-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 4-(tert-butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-1,4-oxazepane-4,6-dicarboxylate.

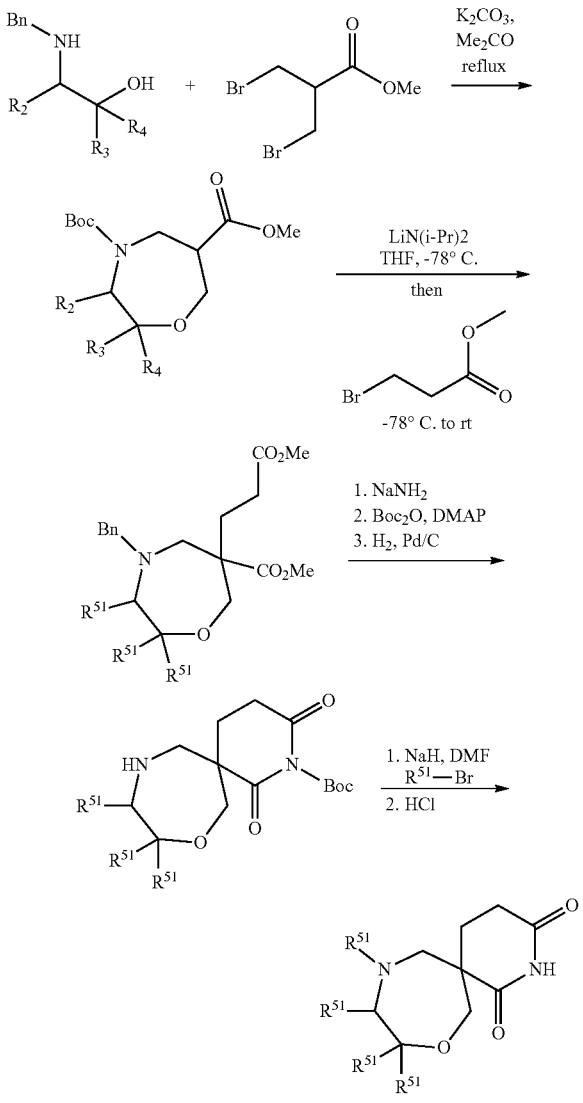
8-Oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 4-(tert-butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-1,4-oxazepane-4,6-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography. *Synthesis,* 1985, (4), 402-403.

The Boc-protected amine is then dissolved in dioxane. HCl (4.0 M in dioxane, 10 equiv.) is then added and the mixture is allowed to stir for 12 hours. The reaction is then concentrated to dryness and the crude material is purifyed on silica yielding 8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione.

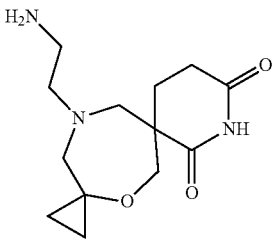
General scheme



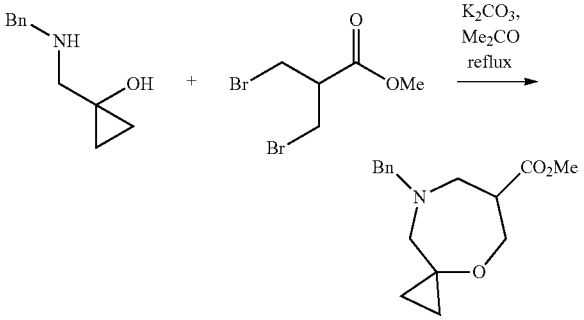
R^{51} is independently selected from H, Alk, Ar, HetAr

R^{51} is independently selected from H, Alk, Ar, HetAr

Representative Synthesis 3: 13-(2-aminoethyl)-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-7,9-dione

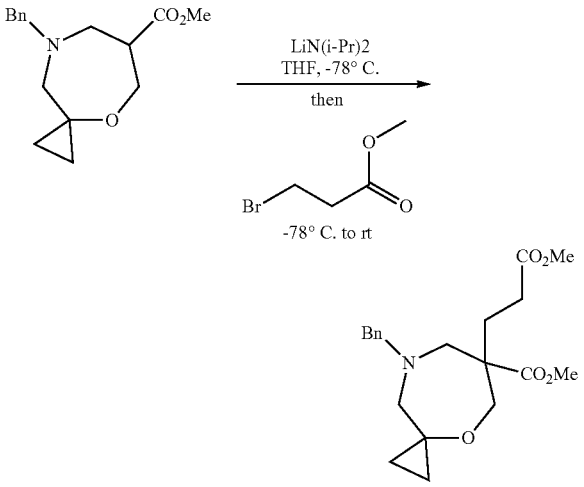


Methyl 8-benzyl-4-oxa-8-azaspiro[2.6]nonane-6-carboxylate



A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), 1-((benzylamino)methyl)cyclopropan-1-ol (1 equiv.), and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired cyclized adduct. PCT Int. Appl., 2010139481.

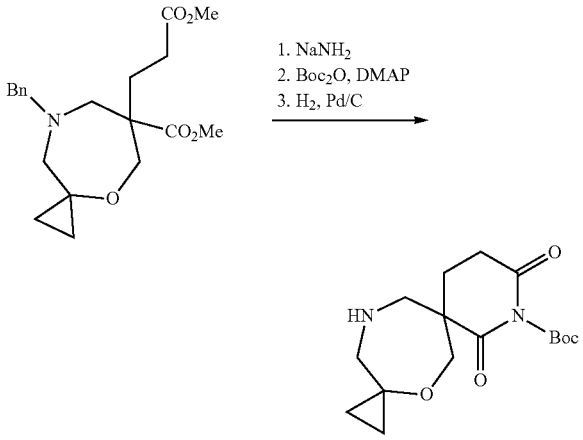
Methyl 8-benzyl-6-(3-methoxy-3-oxopropyl)-4-oxa-8-azaspiro[2.6]nonane-6-carboxylate



Methyl 8-benzyl-4-oxa-8-azaspiro[2.6]nonane-6-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified

on silica providing methyl 8-benzyl-6-(3-methoxy-3-oxopropyl)-4-oxa-8-azaspiro[2.6]nonane-6-carboxylate.

Tert-Butyl 7,9-dioxo-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-8-carboxylate

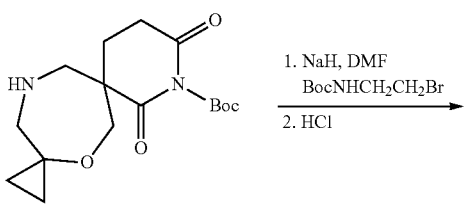


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 8-benzyl-6-(3-methoxy-3-oxopropyl)-4-oxa-8-azaspiro[2.6]nonane-6-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example *Synthesis,* 1985, (4), 402-403.

The free cyclized adduct is then dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The resulting crude material is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding tert-butyl 7,9-dioxo-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-8-carboxylate.

13-(2-Aminoethyl)-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-7,9-dione



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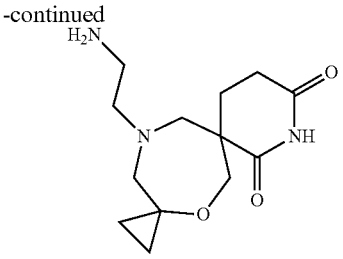
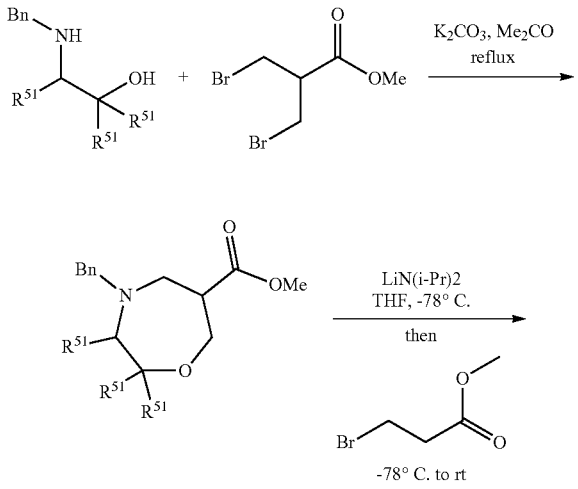
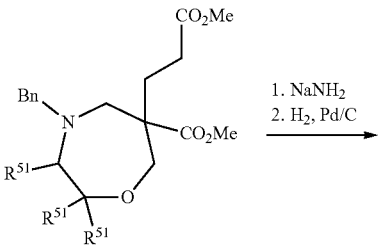


tert-Butyl 7,9-dioxo-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-8-carboxylate (1 equiv.) is dissolved in DMF and added to a suspension of sodium hydride (1.05 equiv., 60% dispersion in mineral oil) and potassium iodide (1 equiv.) in DMF. The mixture is stirred for 90 minutes. tert-butyl (2-bromoethyl)carbamate (1.1 equiv.) in a solution of DMF is then added to the reaction mixture which is stirred at 55° C. The mixture is stirred until the starting material is consumed as judged by TLC or LCMS analysis. The volatiles are then removed under reduced pressure and the residue is redissolved in ethyl acetate and washed with water. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure.

The Boc-protected amine is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and purified on silica to afford 13-(2-aminoethyl)-4-oxa-8,13-diazadispiro[2.2.5^6.3^3]tetradecane-7,9-dione.

General Scheme





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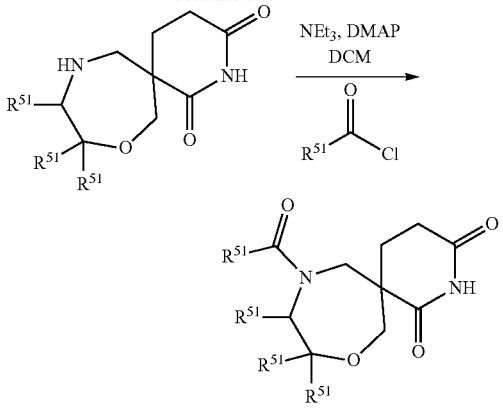
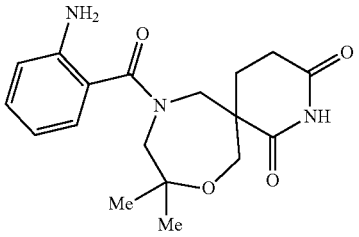
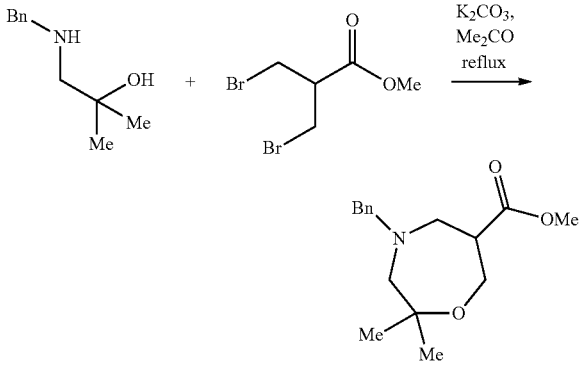


Representative Synthesis 4: 11-(2-Aminobenzoyl)-9,9-dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione

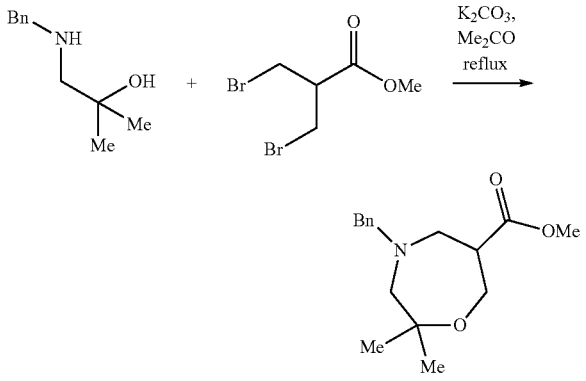


Methyl 4-benzyl-2,2-dimethyl-1,4-oxazepane-6-carboxylate



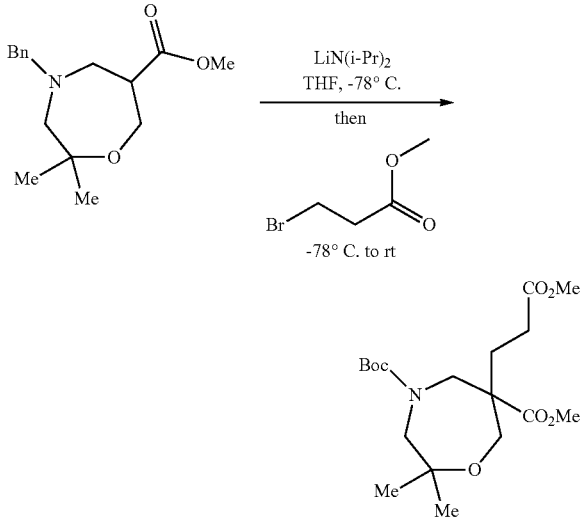
A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), 1-(benzylamino)-2-methylpropan-2-ol (1 equiv.), and potassium carbonate is dissolved in acetone. The solution is heated to reflux and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired cyclized adduct see for example PCT Int. Appl., 2010139481.

Methyl 4-benzyl-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-1,4-oxazepane-6-carboxylate

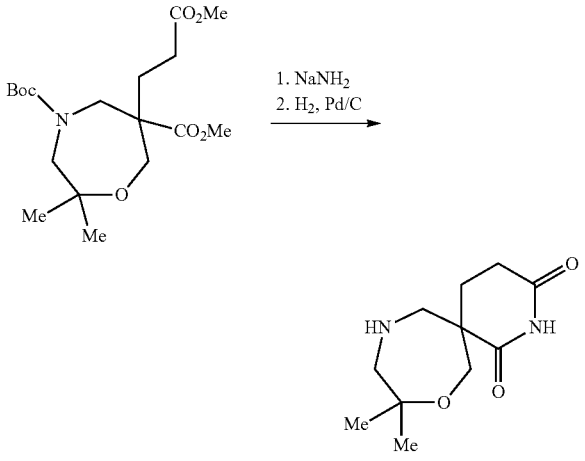


Methyl 4-benzyl-2,2-dimethyl-1,4-oxazepane-6-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 4-benzyl-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-1,4-oxazepane-6-carboxylate.

Methyl 4-benzyl-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-1,4-oxazepane-6-carboxylate

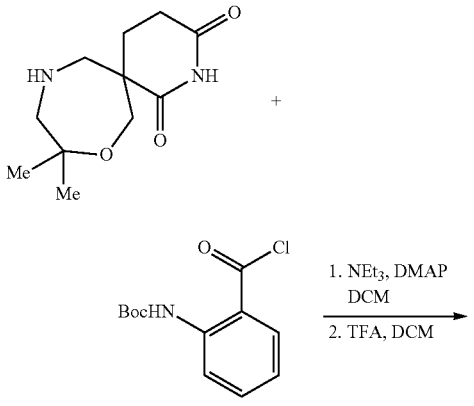


9,9-Dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 4-benzyl-6-(3-methoxy-3-oxopropyl)-2,2-dimethyl-1,4-oxazepane-6-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example *Synthesis,* 1985, (4), 402-403. The resulting spirocyclic compound is then dissolved in methanol. Palladium on carbon (10% by wt) is added and hydrogen gas is bubbled through the reaction mixture. When the reaction is judged complete by TLC or LCMS analysis, the reaction vessel is flushed with nitrogen. The palladium is filtered off and the filtrate is concentrated to dryness before purifying on silica yielding 9,9-dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione.

11-(2-Aminobenzoyl)-9,9-dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione



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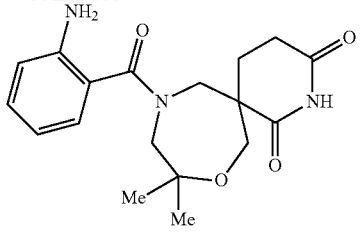
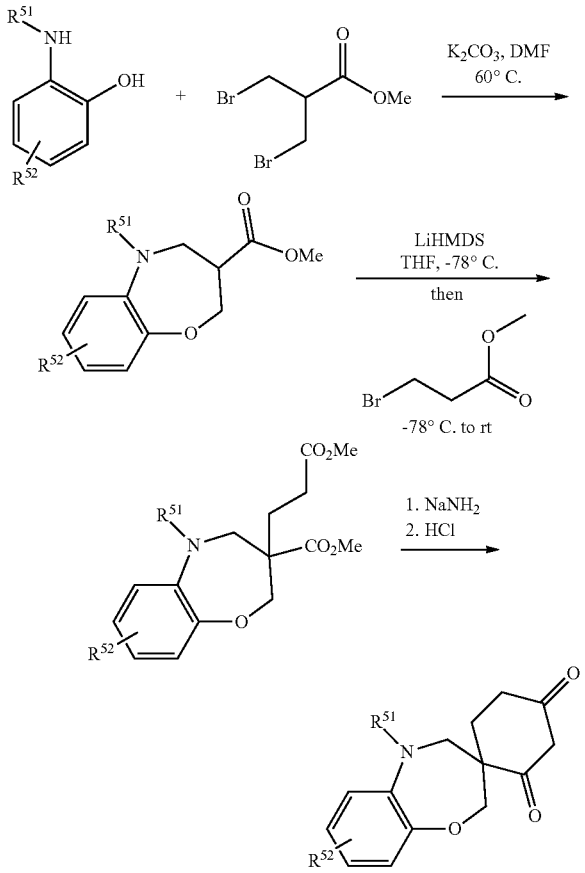


9,9-Dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione (1 equiv.) is dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The resulting crude material was dissolved in a 1:1 mixture of dichloromethane and trifluoroacetic acid. The mixture was allowed to stir for 1 hour and was then concentrated to dryness. The resulting material was purified on silica to afford 11-(2-aminobenzoyl)-9,9-dimethyl-8-oxa-2,11-diazaspiro[5.6]dodecane-1,3-dione.

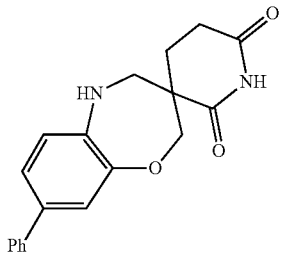
General Scheme



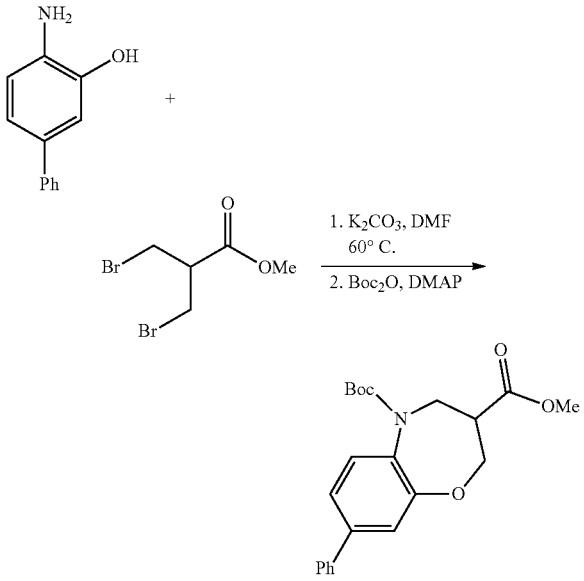
R^{51} is independently selected from —H, alkyl, aryl, heteroaryl;

R^{52} is independently selected from —H, —F, —Cl, —Br, alkyl, aryl, heteroaryl, —OH, —OMe, —NHMe, —NH_2

Representative Synthesis 5: 8-Phenyl-4,5-dihydro-2H-spiro[benzo[b] [1,4]oxazepine-3,3'-piperidine]-2',6'-dione



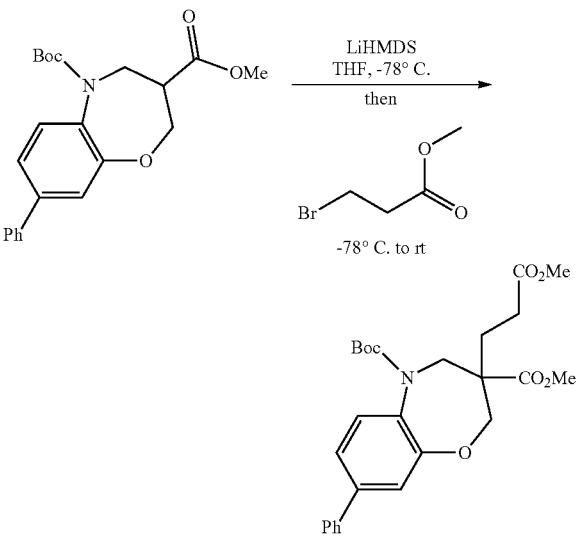
5-(tert-Butyl) 3-methyl 8-phenyl-3,4-dihydrobenzo [b][1,4]oxazepine-3,5(2H)-dicarboxylate



A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), 1-(benzylamino)-2-methylpropan-2-ol (1 equiv.), and potassium carbonate is dissolved in N,N-dimethylformamide. The solution is heated to 60° C. and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give the desired cyclized adduct see for example *European Journal of Medicinal Chemistry,* 2016, 122, 488-496.

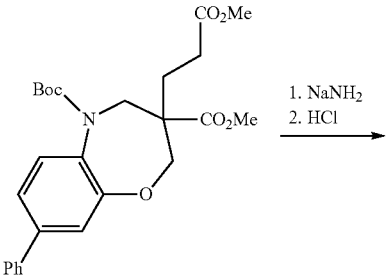
The free cyclized adduct is then dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating to afford 5-(tert-butyl) 3-methyl 8-phenyl-3,4-dihydrobenzo[b][1,4] oxazepine-3,5(2H)-dicarboxylate.

5-(tert-Butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-8-phenyl-3,4-dihydrobenzo[b][1,4]oxazepine-3,5 (2H)-dicarboxylate



5-(t-Butyl) 3-methyl 8-phenyl-3,4-dihydrobenzo[b][1,4] oxazepine-3,5(2H)-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 5-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-8-phenyl-3,4-dihydrobenzo[b][1,4]oxazepine-3,5(2H)-dicarboxylate.

8-Phenyl-4,5-dihydro-2H-spiro[benzo[b][1,4] oxazepine-3,3'-piperidine]-2',6'-dione



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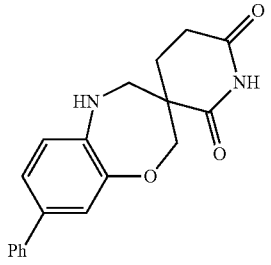
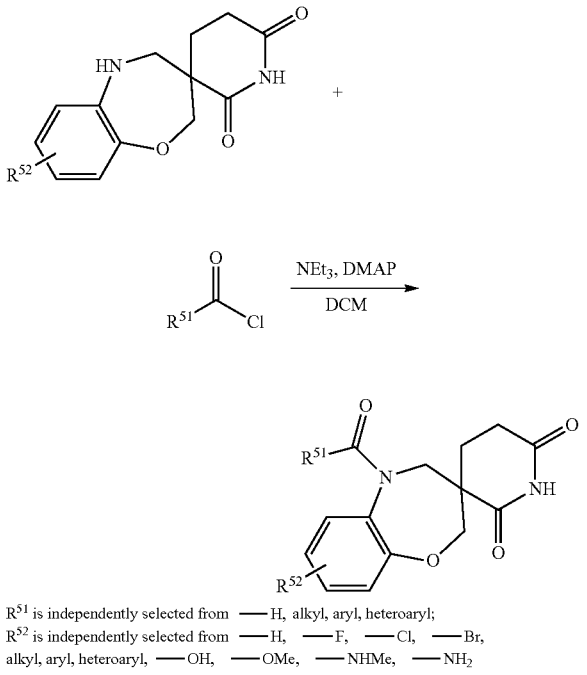


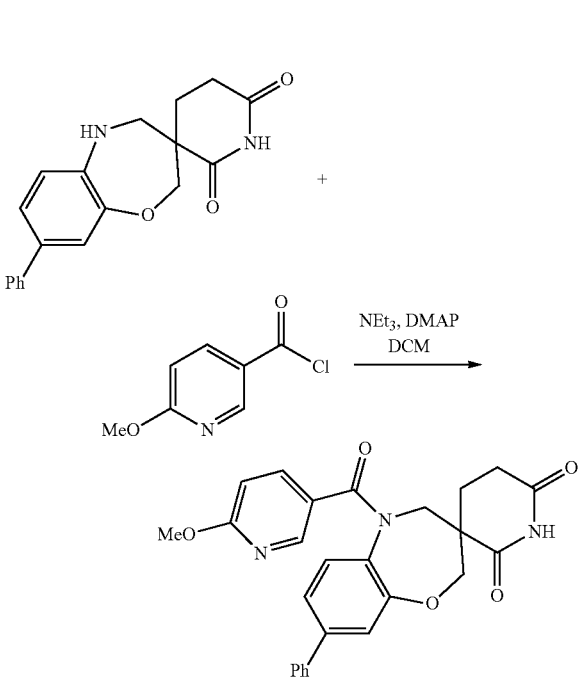
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 5-(tert-butyl) 3-methyl 3-(3-methoxy-3-oxopropyl)-8-phenyl-3,4-dihydrobenzo[b][1,4] oxazepine-3,5(2H)-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example *Synthesis,* 1985, (4), 402-403. The Boc-protected adduct is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude material is purified on silica to afford 8-phenyl-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione.

General Scheme



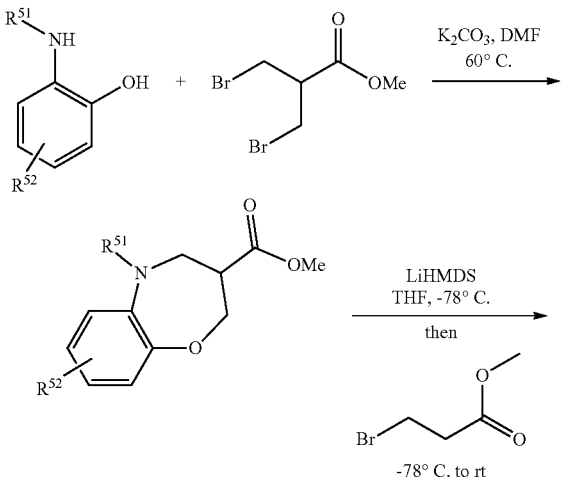
R^{51} is independently selected from —H, alkyl, aryl, heteroaryl;
R^{52} is independently selected from —H, —F, —Cl, —Br, alkyl, aryl, heteroaryl, —OH, —OMe, —NHMe, —NH_2

Example: 5-(6-Methoxynicotinoyl)-8-phenyl-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione



8-Phenyl-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione (1 equiv.) is dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material was purified on silica to afford 5-(6-methoxynicotinoyl)-8-phenyl-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione.

General Scheme



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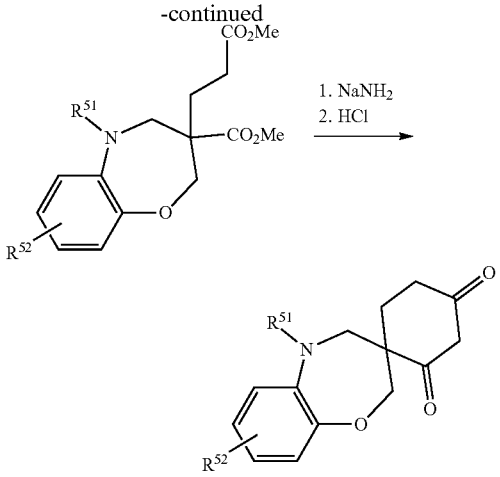
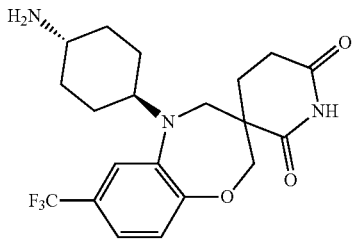
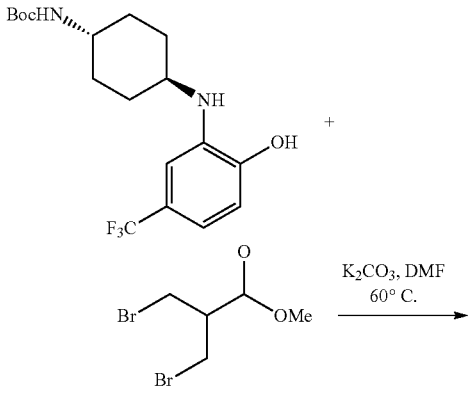


R^{51} is independently selected from —H, —alkyl, —aryl, —heteroaryl;
R^{52} is independently selected from —H, —F, —Cl, —Br, —alkyl, —aryl, —heteroaryl, —OH, —OMe, —NHMe, —NH_2

Representative Synthesis 6: 5-((1r,4r)-4-Aminocyclohexyl)-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione



Methyl 5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate



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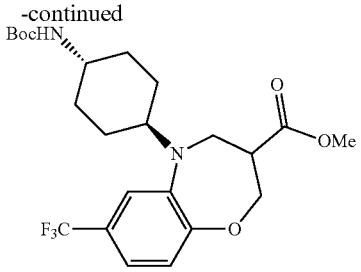
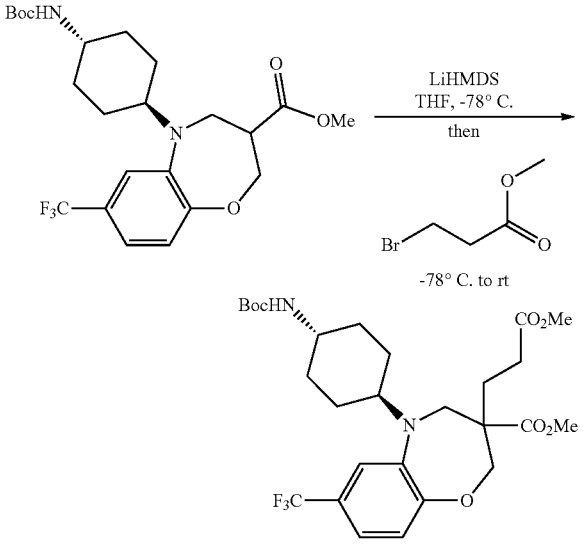


A mixture of methyl 3-bromo-2-(bromomethyl)propanoate (1.2 equiv.), tert-butyl ((1r,4r)-4-((2-hydroxy-5-(trifluoromethyl)phenyl)amino)cyclohexyl)carbamate (1 equiv.), and potassium carbonate is dissolved in N,N-dimethylformamide. The solution is heated to 60° C. and allowed to stir until the starting material is consumed as judged by TLC or LCMS analysis. The mixture is then cooled to room temperature and filtered. The filtrate is evaporated under reduced pressure to give methyl 5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate see for example *European Journal of Medicinal Chemistry,* 2016, 122, 488-496.

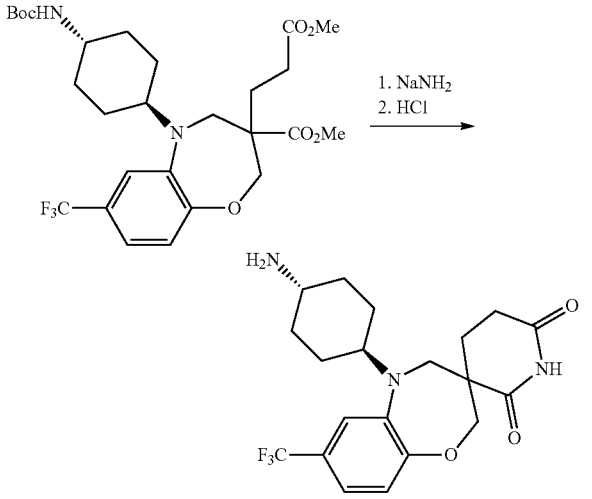
Methyl 5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(3-methoxy-3-oxopropyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate



Methyl-5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is

extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(3-methoxy-3-oxopropyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate.

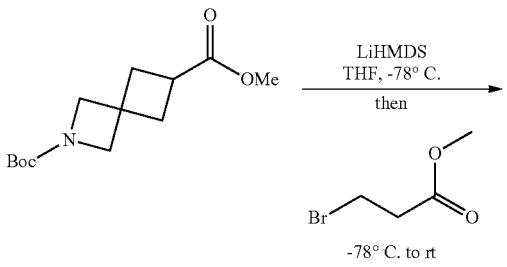
5-((1r,4r)-4-Aminocyclohexyl)-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl-5-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl)-3-(3-methoxy-3-oxopropyl)-7-(trifluoromethyl)-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine-3-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example *Synthesis,* 1985, (4), 402-403.

The Boc-protected adduct is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude material is purified on silica to afford 5-((1r,4r)-4-aminocyclohexyl)-7-(trifluoromethyl)-4,5-dihydro-2H-spiro[benzo[b][1,4]oxazepine-3,3'-piperidine]-2',6'-dione.

General Scheme



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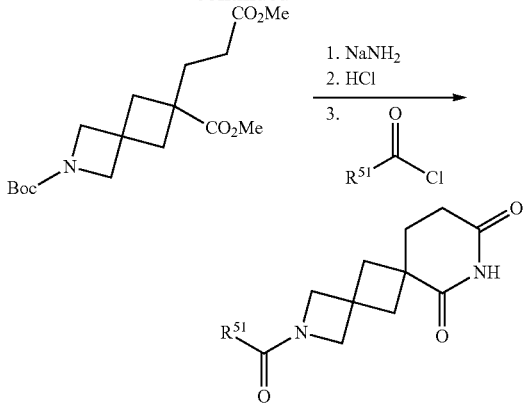
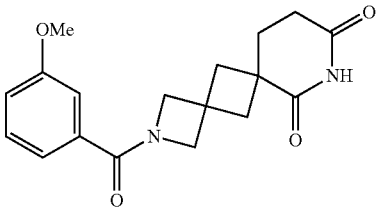
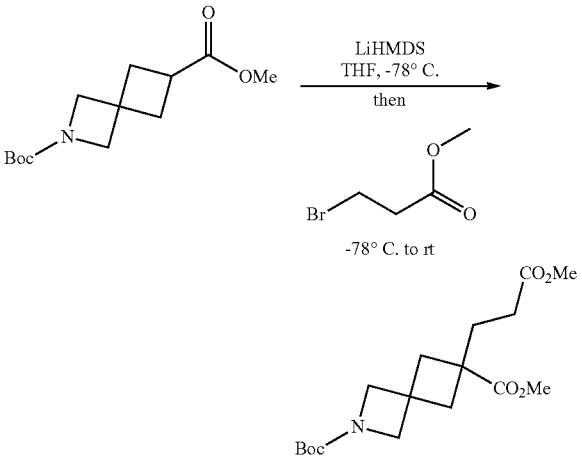


R^{51} is independently selected from alkyl, aryl, and heteroaryl

Representative Synthesis 7: 2-(3-Methoxybenzoyl)-2,8-diazadispiro[3.1.5^6.1^4]dodecane-7,9-dione



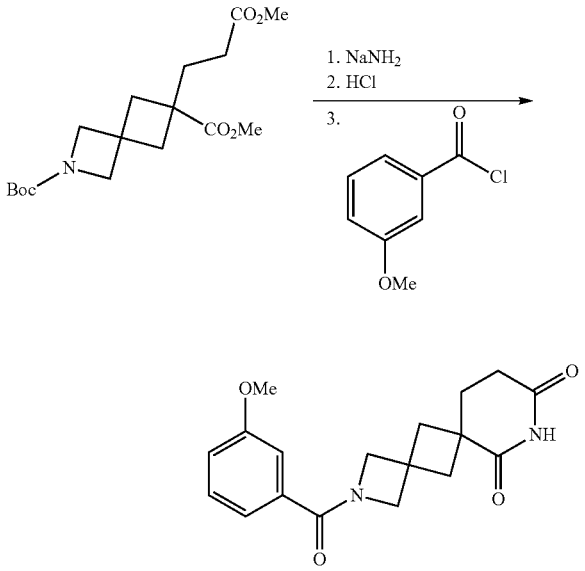
2-(tert-Butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-2-azaspiro[3.3]heptane-2,6-dicarboxylate



2-(t-Butyl) 6-methyl 2-azaspiro[3.3]heptane-2,6-dicarboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis,

it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing 2-(tert-butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-2-azaspiro[3.3]heptane-2,6-dicarboxylate.

2-(3-Methoxybenzoyl)-2,8-diazadispiro[3.1.5^6.1^4] dodecane-7,9-dione

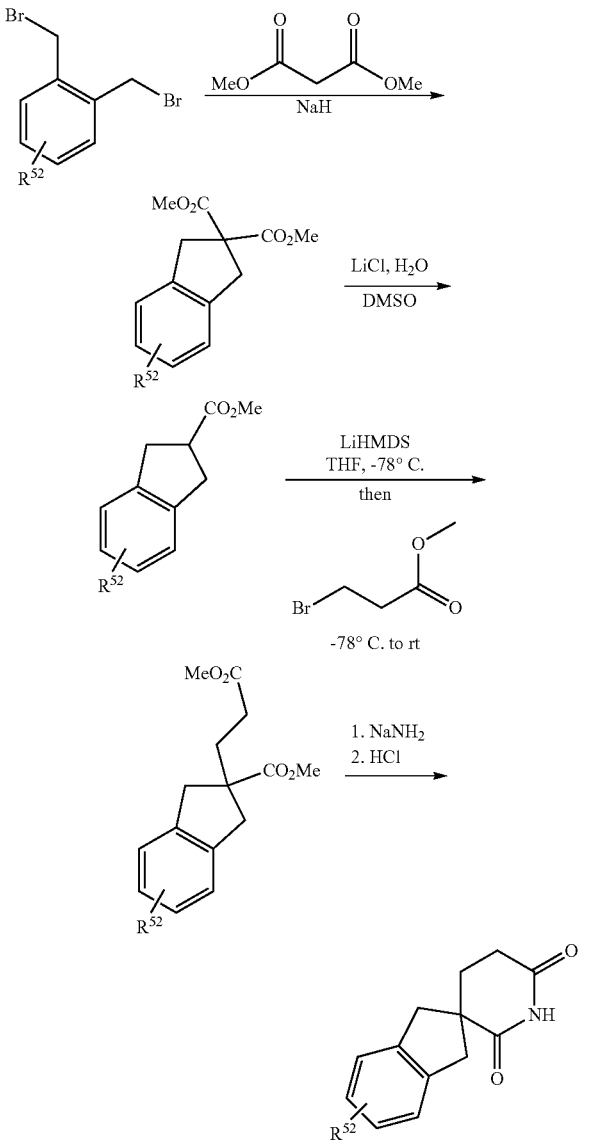


To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the 2-(tert-butyl) 6-methyl 6-(3-methoxy-3-oxopropyl)-2-azaspiro[3.3]heptane-2,6-dicarboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example *Synthesis,* 1985, (4), 402-403.

The Boc-protected adduct is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure.

The free amine (1 equiv.) is then dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is purified on silica to afford 2-(3-methoxybenzoyl)-2,8-diazadispiro [3.1.5^6.1^4]dodecane-7,9-dione.

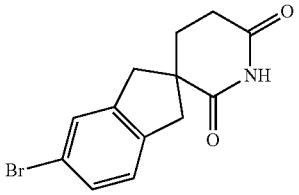
General Scheme



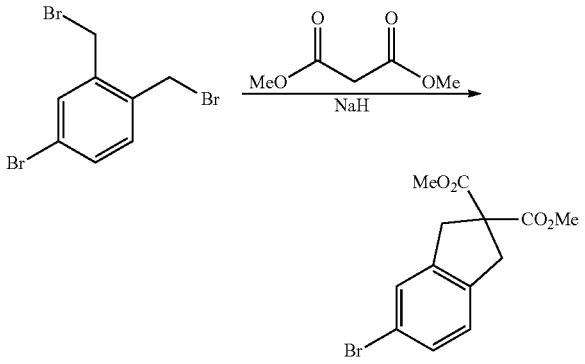
R^{52} is independently select from H, F, Cl, Br, Alkyl, Ar, HetAr, OMe, NMeBoc

R^{52} is independently select from H, F, Cl, Br, Alkyl, Ar, HetAr, OMe, NMeBoc

Representative Synthesis 8: 5-Bromo-1,3-dihydrospiro[indene-2,3'-piperidine]-2',6'-dione

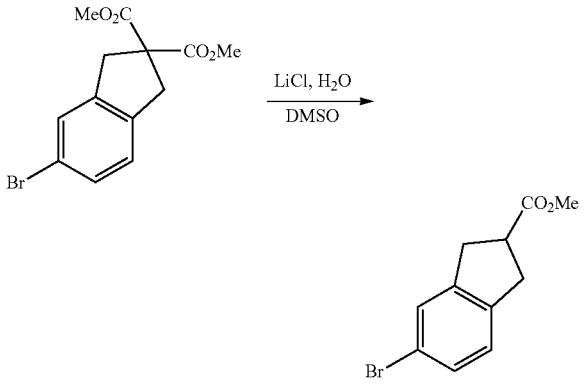


Dimethyl
5-bromo-1,3-dihydro-2H-indene-2,2-dicarboxylate



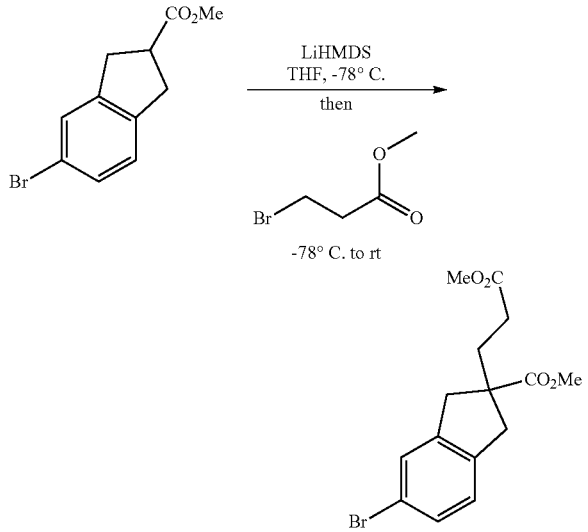
Sodium hydride (60% in mineral oil, 2 equiv.) is added in small portions a 3:1 mixture of ethanol in diethyl ether at room temperature under N_2. After the addition is complete, the solution is stirred for 5 min. To this solution, dimethyl malonate (1 equiv.) is added followed by the addition of 4-bromo-1,2-bis(bromomethyl)benzene (1 equiv.). The resulting mixture is stirred at room temperature for 30 minutes. The reaction mixture is filtered, and the filtrate is concentrated. The residue was purified on silica gel column using 0-10% EtOAc in petroleum ether to afford the title compound see for example PCT Int. Appl., 2012037411, 22 Mar. 2012.

Methyl
5-bromo-2,3-dihydro-1H-indene-2-carboxylate



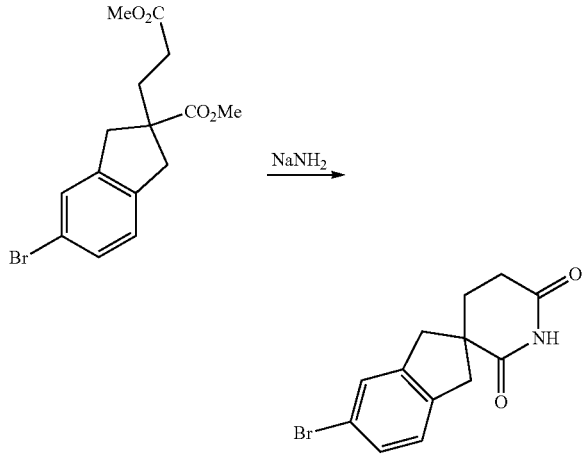
5-Bromo-1,3-dihydro-2H-indene-2,2-dicarboxylic acid (1 equiv.) is dissolved in a 10:1 mixture of DMSO and water. Lithium chloride (3 equiv.) is added and the mixture is stirred overnight to 160° C. The solution is then cooled to room temperature and diluted with water and ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combine organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material was purified on silica to provide methyl 5-bromo-2,3-dihydro-1H-indene-2-carboxylate see for example PCT Int. Appl., 2012037411, 22 Mar. 2012.

Methyl 5-bromo-2-(3-methoxy-3-oxopropyl)-2,3-dihydro-1H-indene-2-carboxylate



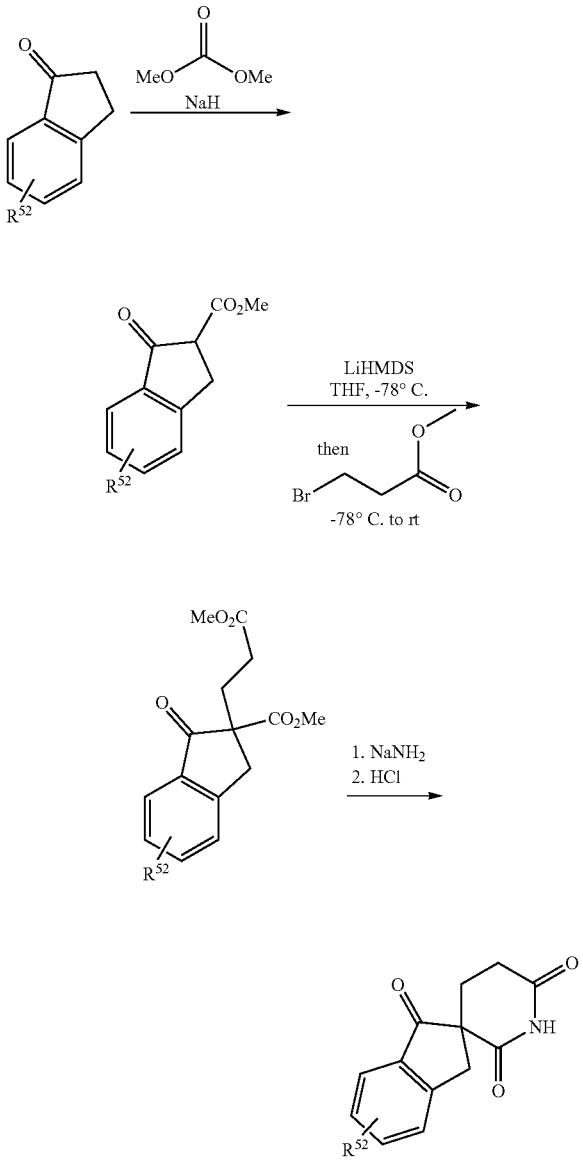
Methyl 5-bromo-2,3-dihydro-1H-indene-2-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 5-bromo-2-(3-methoxy-3-oxopropyl)-2,3-dihydro-1H-indene-2-carboxylate.

5-Bromo-1,3-dihydrospiro[indene-2,3'-piperidine]-2',6'-dione



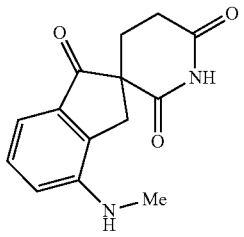
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 5-bromo-2-(3-methoxy-3-oxopropyl)-2,3-dihydro-1H-indene-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h, excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide 5-bromo-1,3-dihydrospiro[indene-2,3'-piperidine]-2',6'-dione see for example *Synthesis,* 1985, (4), 402-403.

General Scheme

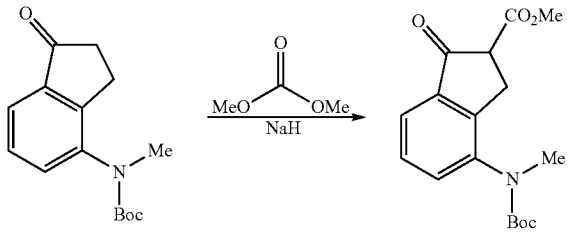


R^{52} is independently selected from H, F, Cl, Alkyl, Ar, HetAr, OMe, NHMe

Representative Synthesis 9: 4-(Methylamino)spiro[indene-2,3'-piperidine]-1,2',6'(3H)-trione

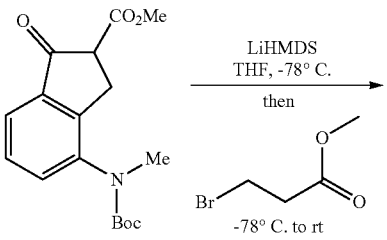


Methyl 4-((tert-butoxycarbonyl)(methyl)amino)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate



t-Butyl methyl(1-oxo-2,3-dihydro-1H-inden-4-yl)carbamate (1 equiv) is dissolved in THF. NaH (60% dispersion in mineral oil, 3 equiv.) is added followed by a solution of dimethyl carbonate (2 equiv.) in THF. The reaction mixture is refluxed for 24 h. The mixture is cooled to room temperature and it is acidified with glacial acetic acid. Aqueous solution of sodium carbonate is added to the mixture and then it is extracted with ethyl acetate. The combined organic phases were washed with water and dried over sodium sulfate. The solvent is evaporated and the resulting crude material is purified on silica providing methyl 4-((tert-butoxycarbonyl)(methyl)amino)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate see for example *Synthetic Communications,* 2015, 45(1), 78-85.

Methyl 4-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate



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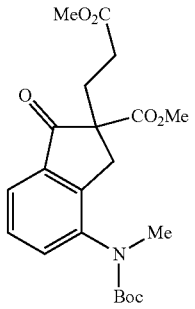
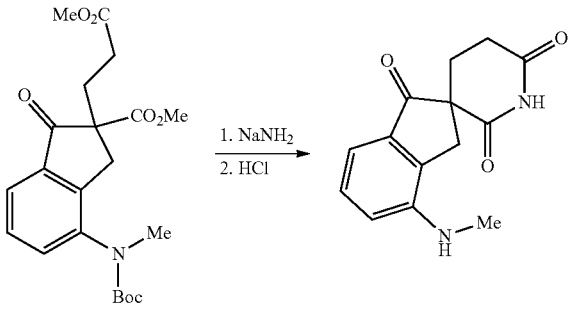


Methyl 4-((tert-butoxycarbonyl)(methyl)amino)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 4-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate.

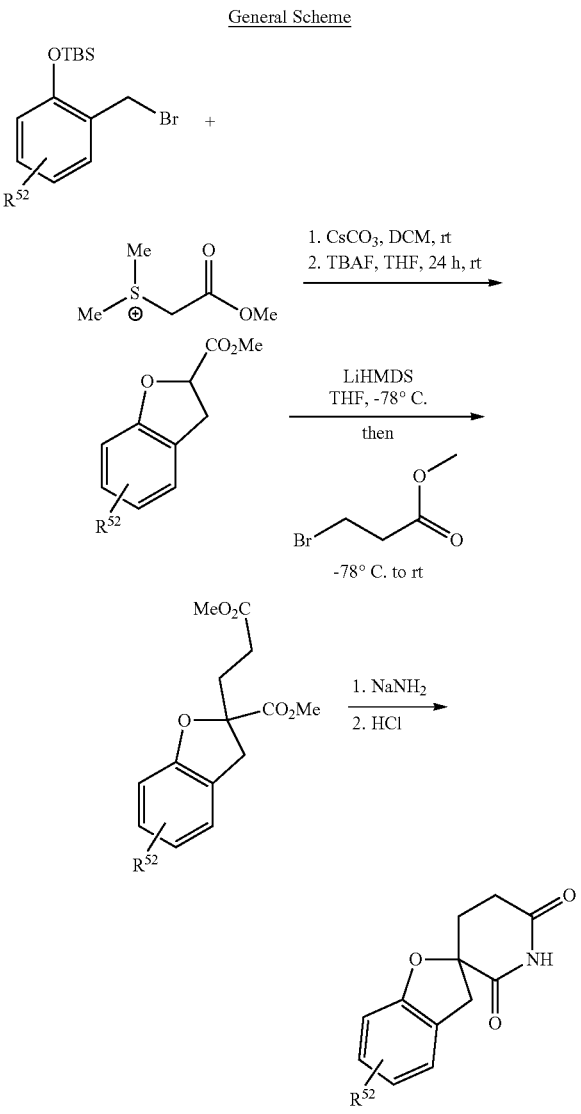
4-(Methylamino)spiro[indene-2,3'-piperidine]-1,2',6'(3H)-trione



To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 4-((tert-butoxycarbonyl)(methyl)amino)-2-(3-methoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h. Excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography see for example Synthesis, 1985, (4), 402-403.

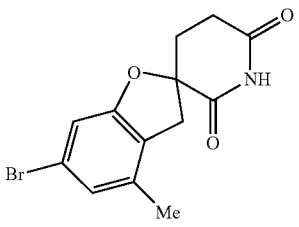
The Boc-protected adduct is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude material is purified on silica to afford 4-(methylamino)spiro[indene-2,3'-piperidine]-1,2',6'(3H)-trione.

General Scheme

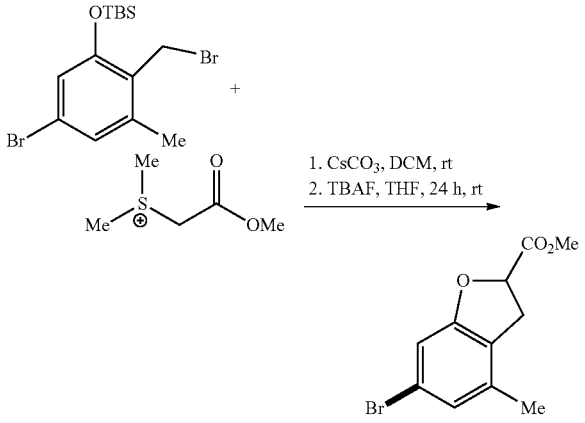


R^{52} is independently selected from H, F, Cl, Br, Alkyl, Ar, HetAr, OMe, NHMe

Representative Synthesis 10: 6-Bromo-4-methyl-3H-spiro[benzofuran-2,3'-piperidine]-2',6'-dione

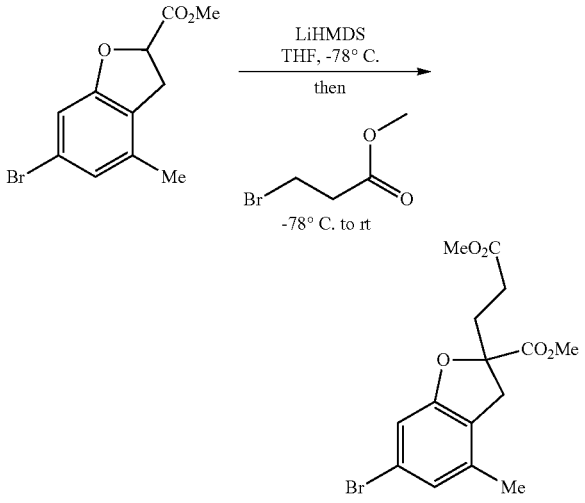


Methyl 6-bromo-4-methyl-2,3-dihydrobenzofuran-2-carboxylate



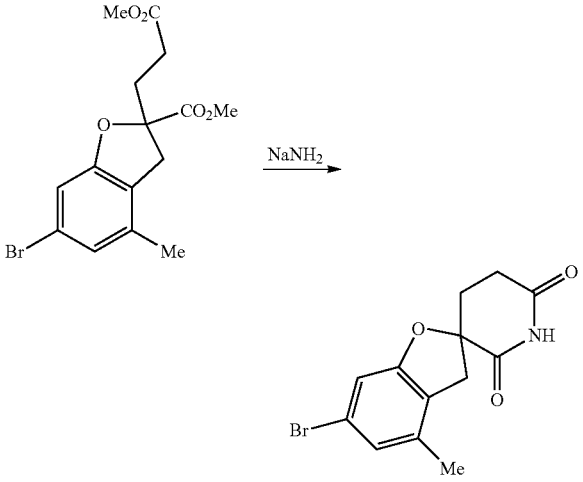
Silylated phenol (1.0 equiv.), sulfonium salt (1.5 equiv.) and cesium carbonate (1.5 equiv.) are stirred in dry dichloromethane at room temperature. After 1h, tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 2.5 equiv.) is added dropwise to the reaction mixture. The reaction is allowed to stir for 24 hours at room temperature. The solvent is then evaporated and the crude material is purified on silica using a gradient of ethyl acetate in hexanes to afford the desired dihydrobenzofuran ester see for example *RSC Advances,* 2015, 5(20), 14953-14957.

Methyl 6-bromo-2-(3-methoxy-3-oxopropyl)-4-methyl-2,3-dihydrobenzofuran-2-carboxylate



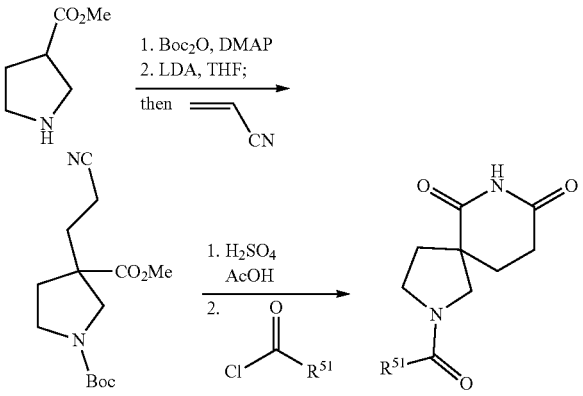
Methyl 6-bromo-4-methyl-2,3-dihydrobenzofuran-2-carboxylate (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl 3-bromopropanoate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 6-bromo-2-(3-methoxy-3-oxopropyl)-4-methyl-2,3-dihydrobenzofuran-2-carboxylate.

6-Bromo-4-methyl-3H-spiro[benzofuran-2,3'-piperidine]-2',6'-dione



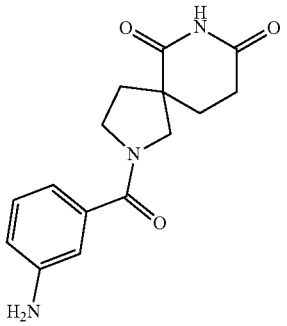
To a stirred solution of sodium amide, prepared in situ from sodium metal and ammonia in the presence of a catalytic amount iron(III) chloride in liquid ammonia, is added a solution of the methyl 6-bromo-2-(3-methoxy-3-oxopropyl)-4-methyl-2,3-dihydrobenzofuran-2-carboxylate in THF at −33° C. The reaction is mixed for 3 h. Excess ammonium chloride is added and the ammonia is allowed to evaporate. Water is then added to the residue and the mixture is extracted with chloroform. The combined organic layer is dried over sodium sulfate, concentrated and purified by silica gel chromatography to provide 6-bromo-4-methyl-3H-spiro[benzofuran-2,3'-piperidine]-2',6'-dione see for example *Synthesis,* 1985, (4), 402-403.

General Scheme

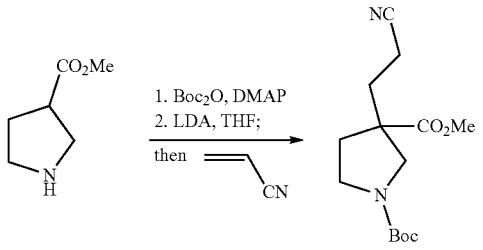


R^{51} is independently selected from Alkyl, Aryl, HetAryl

Representative Synthesis 11: 2-(3-Aminobenzoyl)-2,7-diazaspiro[4.5]decane-6,8-dione



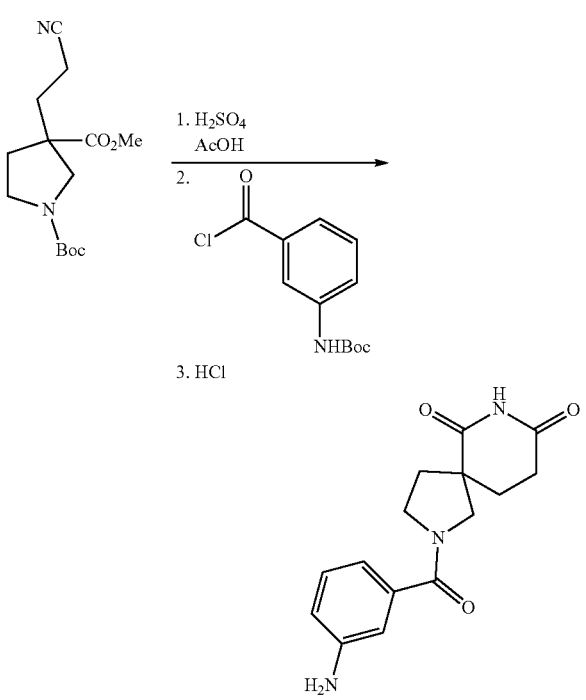
1-(t-Butyl) 3-methyl 3-(2-cyanoethyl)pyrrolidine-1,3-dicarboxylate



Methyl pyrrolidine-3-carboxylate is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The crude material is then dissolved in tetrahydrofuran and cooled to −70° C. This solution is added slowly to a freshly prepared solution of lithium diisopropylamide (1.2 equiv.) at −70° C. The mixture was allowed to stir for 1 hour. Acrylonitrile (1.5 equiv.) was then added dropwise and the mixture was allowed to warm to room temperature overnight. The mixture was then poured onto aqueous ammonium chloride and extracted with ethyl acetate (3×). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was the purified on silica to provide 1-(tert-butyl) 3-methyl 3-(2-cyanoethyl) pyrrolidine-1,3-dicarboxylate see for example U.S. Pat. Appl. Publ., 20120165331, 28 Jun. 2012.

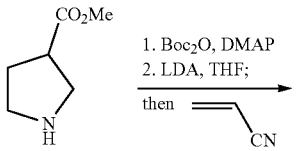
2-(3-Aminobenzoyl)-2,7-diazaspiro[4.5]decane-6,8-dione



1-(t-Butyl) 3-methyl 3-(2-cyanoethyl)pyrrolidine-1,3-dicarboxylate was dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture was heated to reflux for 2 hours. Water was then added to the reaction mixture which was then continued to be heated at reflux for 2 hours. The mixture was then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer was then washed with brine and dried over sodium sulfate before concentrating see for example PCT Int. Appl., 2009157515, 30 Dec. 2009. The free amine (1 equiv.) is then dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure.

The Boc-protected adduct is then dissolved in dioxane. HCl (4N in dioxane, 10 equiv.) is added and the solution stirred at room temperature for 12 hours. The solvent is then evaporated under reduced pressure and the crude material is purified on silica to afford 2-(3-aminobenzoyl)-2,7-diazaspiro[4.5]decane-6,8-dione.

General Scheme



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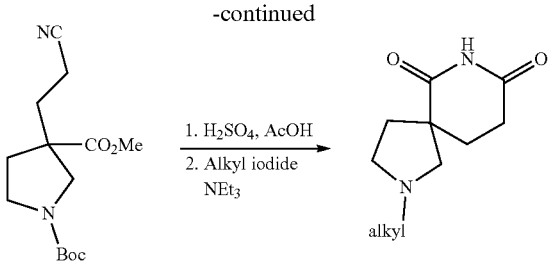
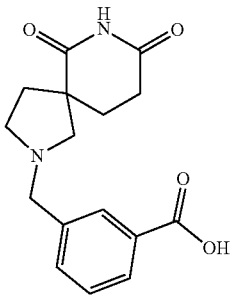
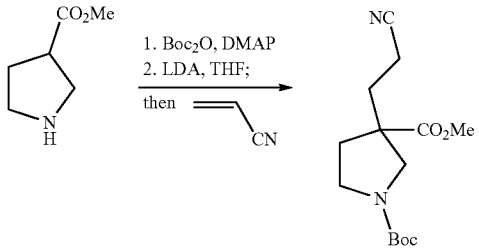


Representative Synthesis 12: 3-((6,8-Dioxo-2,7-diazaspiro[4.5]decan-2-yl)methyl)benzoic acid



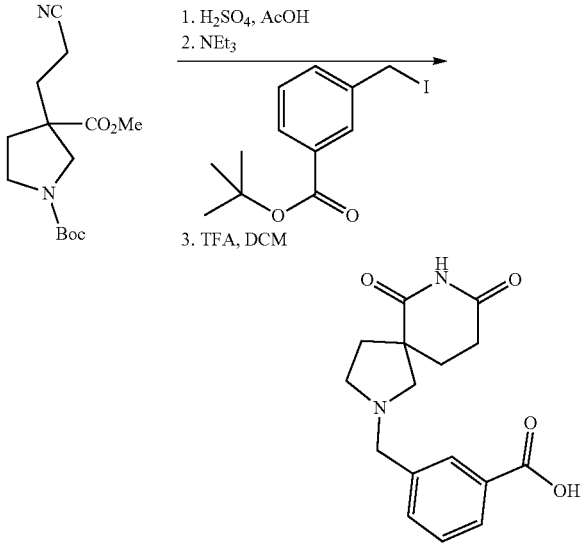
1-(tert-Butyl) 3-methyl 3-(2-cyanoethyl)pyrrolidine-1,3-dicarboxylate



Methyl pyrrolidine-3-carboxylate is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The crude material is then dissolved in tetrahydrofuran and cooled to −70° C. This solution is added slowly to a freshly prepared solution of lithium diisopropylamide (1.2 equiv.) at −70° C. The mixture was allowed to stir for 1 hour. Acrylonitrile (1.5 equiv.) was then added dropwise and the mixture was allowed to warm to room temperature overnight. The mixture was then poured onto aqueous ammonium chloride and extracted with ethyl acetate (3×). The organic layers were combined and washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was the purified on silica to provide 1-(tert-butyl) 3-methyl 3-(2-cyanoethyl) pyrrolidine-1,3-dicarboxylate see for example U.S. Pat. Appl. Publ., 20120165331, 28 Jun. 2012.

3-((6,8-Dioxo-2,7-diazaspiro[4.5]decan-2-yl)methyl) benzoic Acid

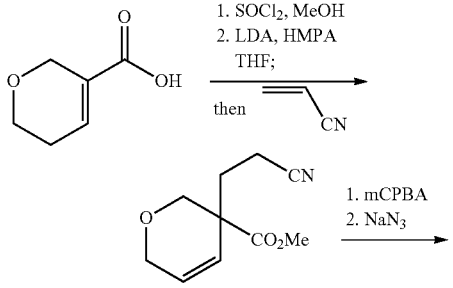


1-(t-Butyl) 3-methyl 3-(2-cyanoethyl)pyrrolidine-1,3-dicarboxylate was dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture was heated to reflux for 2 hours. Water was then added to the reaction mixture which was then continued to be heated at reflux for 2 hours. The mixture was then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer was then washed with brine and dried over sodium sulfate before concentrating see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

The crude material was then dissolved in N,N-dimethylformamide. Triethylamine (2 equiv.) was added followed by alkyl iodide (1 equiv.). The mixture was allowed to stir for 18 hours. It was then diluted with water and extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating.

The resulting tert-butyl ester (1 equiv.) was then dissolved in a 1:1 mixture of DCM and trifluoroacetic acid. The mixture was allowed to stir for 1 hour and then the volatiles were removed under reduced pressure. The crude material was then purified on silica to provide 3-((6,8-dioxo-2,7-diazaspiro[4.5]decan-2-yl)methyl)benzoic acid.

General Scheme:



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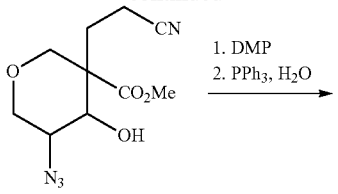
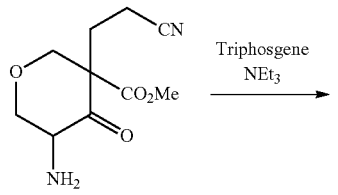
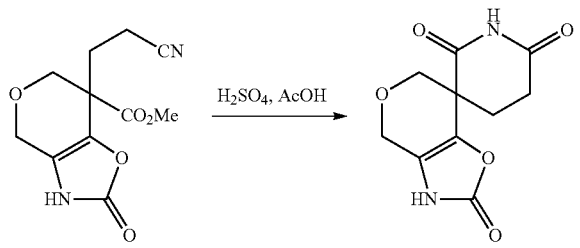
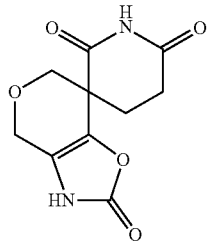


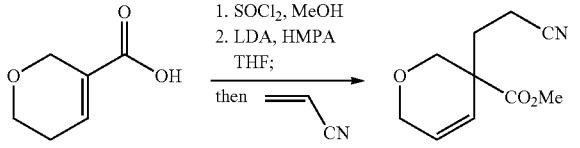




Representative Synthesis 13: 4'H,6'H-spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,2',6(3'H)-trione



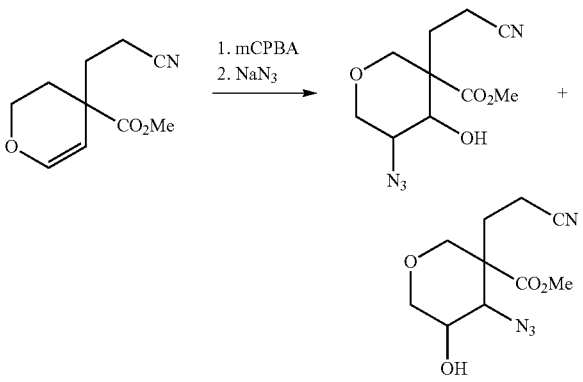
Methyl 3-(2-cyanoethyl)-3,6-dihydro-2H-pyran-3-carboxylate



5,6-Dihydro-2H-pyran-3-carboxylic acid is dissolved in methanol and cooled to 0° C. Thionyl chloride (1 equiv.) was added slowly. The reaction mixture was heated to reflux for 2 hours. It is then cooled to room temperature and diluted with ice water. The mixture is extracted with ethyl acetate (3×) and the combined organic layers are washed with saturated sodium bicarbonate solution and then brine before drying with sodium sulfate. The mixture is then concentrated and purified on silica to provide the desired methyl ester.

To a solution of diisopropylethylamine (1.6 equiv.) in tetrahydrofuran is added n-butyllithium (1.5 equiv.) at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and then cooled to −78° C. Hexamethylphosphorictriamide (1.1 equiv.) was then added. The solution is allowed to stir for 15 minutes before the addition of a tetrahydrofuran solution of methyl 5,6-dihydro-2H-pyran-3-carboxylate (1 equiv.) was added. The mixture is allowed to stirr for 1 h at −78° C. followed by the addiction of acrylonitrile (1.5 equiv.). The mixture is allowed to warm to room temperature across 2 h. It is then diluted with ethyl acetate and washed with 1 M HCl solution, brine, and then dried over sodium sulfate. The mixture is then concentrated and the crude material purified on silica to provide methyl 3-(2-cyanoethyl)-3,6-dihydro-2H-pyran-3-carboxylate see for example PCT Int. Appl., 2015005901, 15 Jan. 2015.

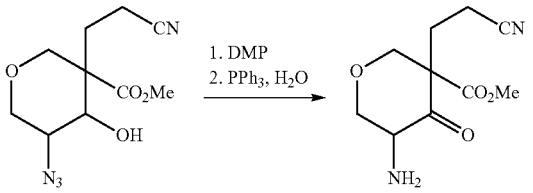
Methyl 5-azido-3-(2-cyanoethyl)-4-hydroxytetrahydro-2H-pyran-3-carboxylate



Methyl-3-(2-cyanoethyl)-3,6-dihydro-2H-pyran-3-carboxylate (1 equiv.) is dissolved in dichloromethane and cooled to 0° C. m-Chloroperbenzoic acid (1.2 equiv.) is added portionwise and the mixture is allowed to stir for 2 hours. It is then quenched with 0.5 M sodium thiosulfate solution. The organic layer is separated and the aqueous layer extracted with dichloromethane (3×). The organic layer is then washed with brine and dried over sodium sulfate before concentrating under reduced pressure affording the desired epoxide.

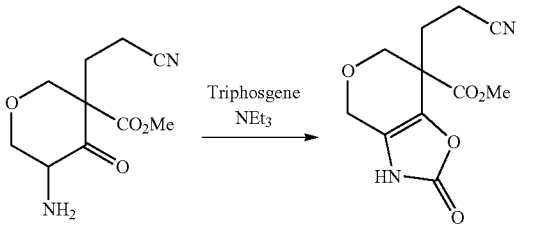
The obtained epoxide is then dissolved in acetonitrile. Sodium azide (1.5 equiv.) is added and the mixture was heated to 80° C. for 12 h. The mixture is then cooled to room temperature and quenched with water. The mixture is extracted with dichloromethane (3×) and the combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude residue is then purified on silica, discarding the undesired regioisomer, to afford methyl 5-azido-3-(2-cyanoethyl)-4-hydroxytetrahydro-2H-pyran-3-carboxylate.

Methyl 5-amino-3-(2-cyanoethyl)-4-oxotetrahydro-2H-pyran-3-carboxylate



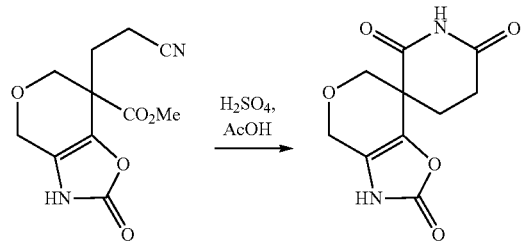
Methyl 5-azido-3-(2-cyanoethyl)-4-hydroxytetrahydro-2H-pyran-3-carboxylate (1 equiv.) is dissolved in dichloromethane. Dess-Martin periodinane (1 equiv.) is added and the mixture is allowed to stir for 2 h. The reaction is then quenched with saturated sodium bicarbonate solution and diluted with dichloromethane. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude azido ketone is then dissolved in dichloromethane triphenylphosphine (1.1 equiv.) was added and the mixture was stirred at room temperature for 2 h. Water is then added to the reaction mixture. After 15 minutes the organic layer is separated and the aqueous layer is extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The resulting crude material is then purified using reverse phase column chromatography to yield methyl 5-amino-3-(2-cyanoethyl)-4-oxotetrahydro-2H-pyran-3-carboxylate see for example U.S. Pat. Appl. Publ., 20070213394, 13 Sep. 2007.

Methyl-7-(2-cyanoethyl)-2-oxo-2,3,6,7-tetrahydro-4H-pyrano[3,4-d]oxazole-7-carboxylate



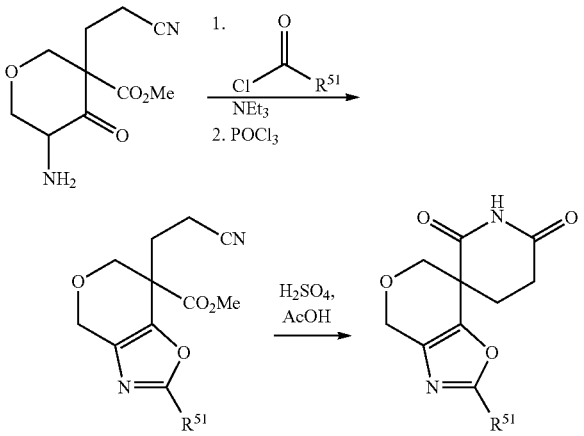
Methyl-5-amino-3-(2-cyanoethyl)-4-oxotetrahydro-2H-pyran-3-carboxylate (1 equiv.) is dissolved in THF. Triethylamine (5 equiv.) is added. The mixture was then cooled to −50° C. Triphosgene is added slowly and the mixture is allowed to stir for 1 hour. The solution is then diluted with diethyl ether and saturated aqueous ammonium chloride solution is added. The aqueous phase was separated and extracted with diethyl ether (3×). The combined organic layers are washed with brine, dried over sodium sulfate, concentrated, and purified on silica to afford methyl 7-(2-cyanoethyl)-2-oxo-2,3,6,7-tetrahydro-4H-pyrano[3,4-d] oxazole-7-carboxylate see for example PCT Int. Appl., 2016096115, 23 Jun. 2016.

4'H,6'H-Spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,2',6(3'H)-trione



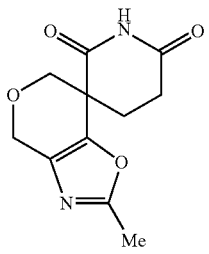
Methyl-7-(2-cyanoethyl)-2-oxo-2,3,6,7-tetrahydro-4H-pyrano[3,4-d]oxazole-7-carboxylate is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is heated at reflux for 2 hours. The mixture is then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer was then washed with brine and dried over sodium sulfate before concentrating to afford 4'H,6'H-spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,2',6(3'H)-trione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme

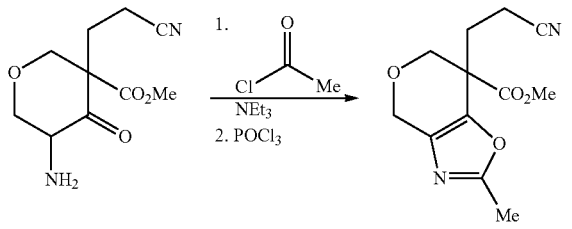


R^{51} is independently selected from H, Alkyl, Aryl, HetAryl

Representative Synthesis 14: 2'-Methyl-4'H,6'H-spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,6-dione



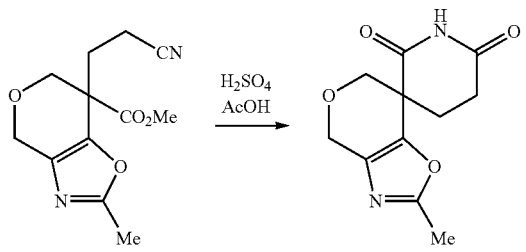
Methyl 7-(2-cyanoethyl)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d]oxazole-7-carboxylate



Methyl-7-(2-cyanoethyl)-2-oxo-2,3,6,7-tetrahydro-4H-pyrano[3,4-d]oxazole-7-carboxylate (1 equiv.) is dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure.

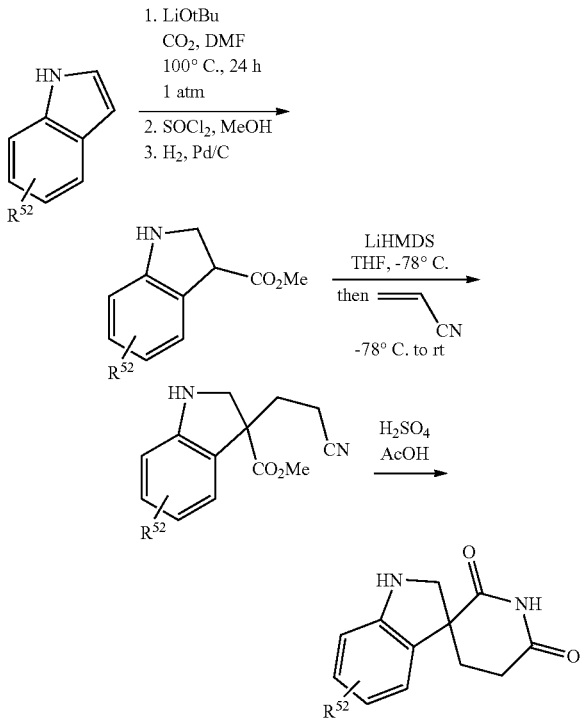
The crude material is then dissolved in benzene. Phosphorous oxychloride (1 equiv.) is then added and the mixture is heated to reflux for 8 h. The reaction is then cooled to room temperature and quenched with saturated sodium bicarbonate aqueous solution. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combine organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is then purified on silica to provide methyl 7-(2-cyanoethyl)-2-methyl-6,7-dihydro-4H-pyrano[3,4-d]oxazole-7-carboxylate see for example PCT Int. Appl., 2004065374, 5 Aug. 2004

2'-Methyl-4'H,6'H-spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,6-dione



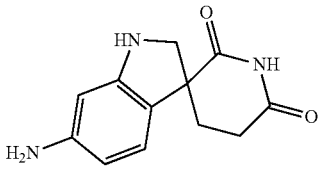
Methyl-7-(2-cyanoethyl)-2-oxo-2,3,6,7-tetrahydro-4H-pyrano[3,4-d]oxazole-7-carboxylate is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is then heated at reflux for 2 hours. The mixture is then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 4'H,6'H-spiro[piperidine-3,7'-pyrano[3,4-d]oxazole]-2,2',6(3'H)-trione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme

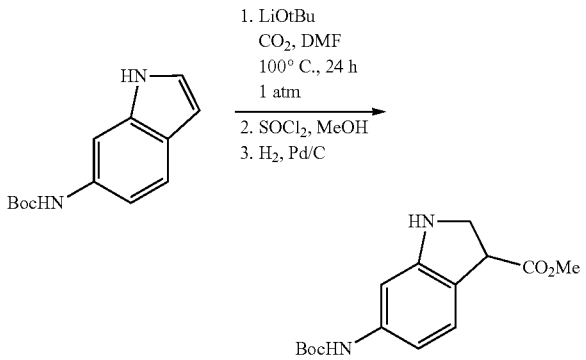


R^{52} is independently selected from H, F, Cl, Alkyl, Aryl, HetAryl, OMe, NH_2

Representative Synthesis 15: 6-Aminospiro[indoline-3,3'-piperidine]-2',6'-dione



Methyl 6-((tert-butoxycarbonyl)amino)indoline-3-carboxylate

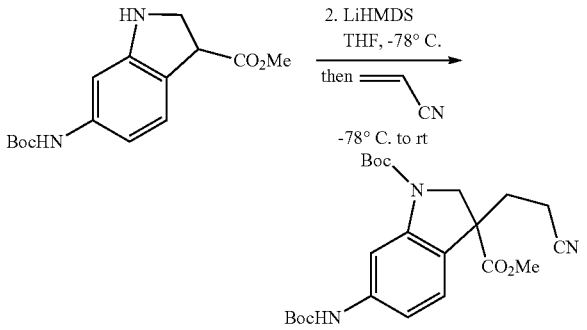


tert-Butyl (1H-indol-6-yl)carbamate (1 equiv.) is dissolved in dry N,N-dimethylformamide. Lithium tert-butoxide (5 equiv.) is added. Carbon dioxide is bubbled through the solution which is then heated to 100° C. After 24 h, the reaction is cooled to room temperature and quenched with saturated ammonium chloride aqueous solution. The mixture is diluted with ethyl acetate and the organic layer is separated. The aqueous layer is extracted with ethyl acetate (3×) and the combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The resulting carboxylic acid is then dissolved in methanol and cooled to 0° C. Thionyl chloride (1 equiv.) is added slowly. The reaction mixture is heated to reflux for 2 hours. It is then cooled to room temperature and diluted with ice water. The mixture is extracted with ethyl acetate (3×) and the combined organic layers are washed with saturated sodium bicarbonate solution and then brine before drying with sodium sulfate. The mixture is concentrated and purified on silica to provide the desired methyl ester.

The methyl ester is then dissolved in methanol. Palladium on carbon (10% by wt) is then added and the solution is degassed 3 times by replacing the air with nitrogen and finally the nitrogen with hydrogen. The reaction mixture was further stirred under hydrogen atmosphere for 2 h. The hydrogen gas was then purged and the mixture was filtered through a pad of celite and washed with methanol. The solvent was removed under vacuum and the resulting material was purified on silica to provide methyl 6-((tert-butoxycarbonyl)amino)indoline-3-carboxylate.

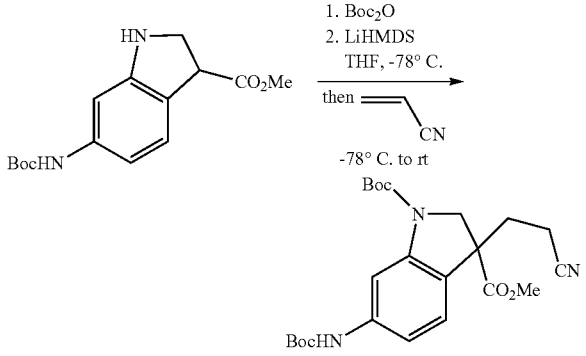
1-(t-Butyl) 3-methyl 6-((tert-butoxycarbonyl) amino)-3-(2-cyanoethyl)indoline-1,3-dicarboxylate



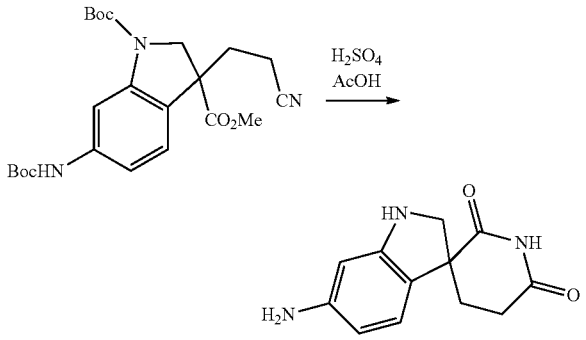
Di-tert-butyl dicarbonate (1.2 equiv.) is dissolved in dry tetrahydrofuran. A solution of indoline (1 equiv.) in tetrahydrofuran is added dropwise via addition funnel at a rate to maintain a steady gas evolution. The mixture is then allowed to stir for a further 3 hours. The mixture is filtered through a small pad of silica and the Boc-protected indoline is used directly in the next step.

To a solution of diisopropylethylamine (1.6 equiv.) in tetrahydrofuran was added n-butyllithium (1.5 equiv.) at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and then cooled to −78° C. Hexamethylphosphorictriamide (1.1 equiv.) was then added. The solution was allowed to stir for 15 minutes before the addition of a tetrahydrofuran solution of methyl 5,6-dihydro-2H-pyran-3-carboxylate (1 equiv.) was added. The mixture stirred for 1 h at −78° C. followed by the addiction of acrylonitrile (1.5 equiv.). The mixture was allowed to warm to room temperature across 2 h. It was then diluted with ethyl acetate and washed with 1 M HCl solution, brine, and then dried over sodium sulfate. The mixture was then concentrated and the crude material was purified on silica to provide 1-(tert-butyl) 3-methyl 6-((tert-butoxycarbonyl)amino)-3-(2-cyanoethyl)indoline-1,3-dicarboxylate see for example PCT Int. Appl., 2015005901, 15 Jan. 2015.

1-(tert-Butyl) 3-methyl 6-((tert-butoxycarbonyl) amino)-3-(2-cyanoethyl)indoline-1,3-dicarboxylate

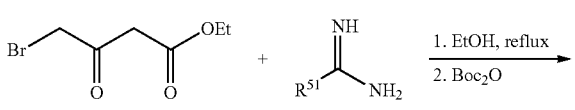


6-Aminospiro[indoline-3,3'-piperidine]-2',6'-dione



1-(tert-Butyl)-3-methyl-6-((tert-butoxycarbonyl)amino)-3-(2-cyanoethyl)indoline-1,3-dicarboxylate is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is heated at reflux for 2 hours. The mixture was then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 6-aminospiro[indoline-3,3'-piperidine]-2',6'-dione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme:



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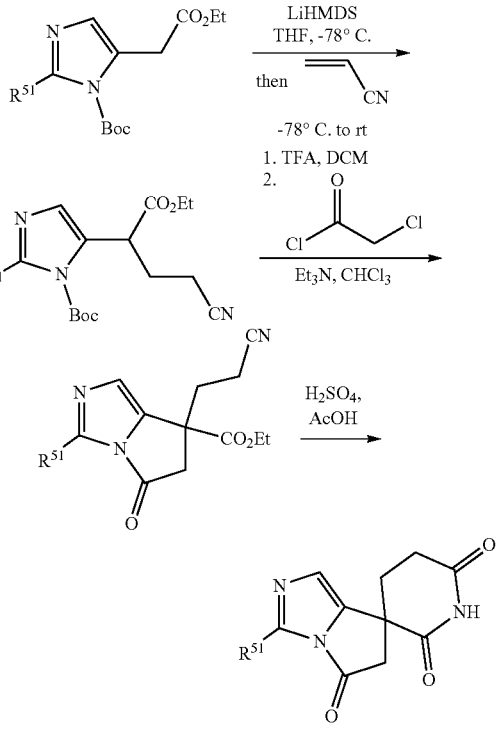
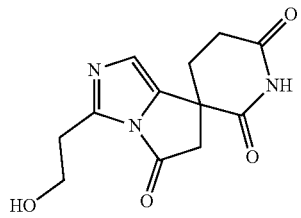
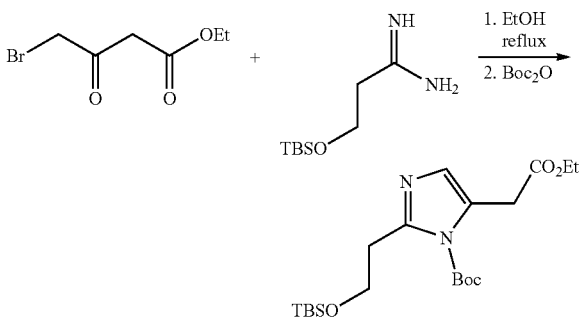


R^{51} is independently selected from H, Alkyl, Aryl, HetAryl

Representative Synthesis 16: 3'-(2-Hydroxyethyl) spiro[piperidine-3,7'-pyrrolo[1,2-c]imidazole]-2,5',6 (6'H)-trione



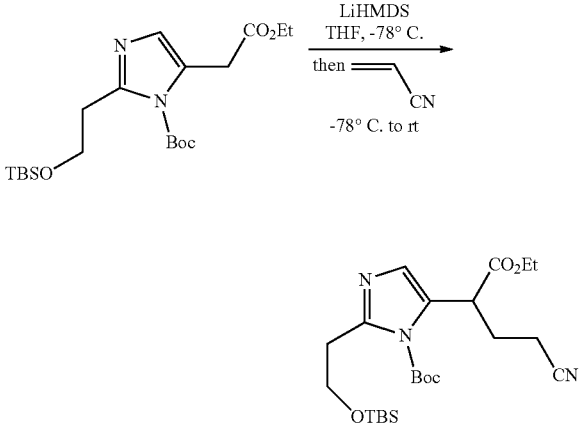
tert-Butyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(2-ethoxy-2-oxoethyl)-1H-imidazole-1-carboxylate



Ethyl 4-bromo-3-oxobutanoate (1 equiv.) and 3-((tert-butyldimethylsilyl)oxy)propanimidamide (1 equiv.) are dissolved in ethanol. The mixture is heated to reflux and allowed to stir for 12 hours. It is then cooled to room temperature and concentrated under vacuum see for example *Journal of Medicinal Chemistry,* 2014, 57(12), 5293-5305.

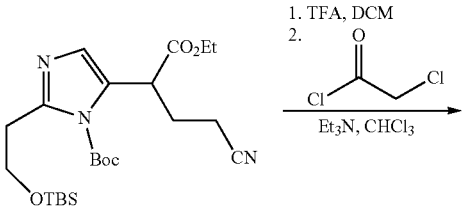
The resulting residue is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is then purified on silica providing tert-butyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(2-ethoxy-2-oxoethyl)-1H-imidazole-1-carboxylate.

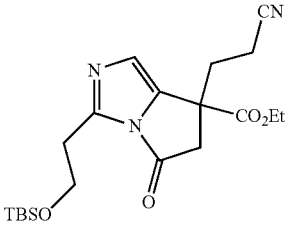
tert-Butyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-1H-imidazole-1-carboxylate



To a solution of diisopropylethylamine (1.6 equiv.) in tetrahydrofuran was added n-butyllithium (1.5 equiv.) at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and then cooled to −78° C. Hexamethylphosphorictriamide (1.1 equiv.) was then added. The solution was allowed to stir for 15 minutes before the addition of a tetrahydrofuran solution of tert-butyl 2-(2-((tert-butyldimethylsilyl)oxy) ethyl)-5-(2-ethoxy-2-oxoethyl)-1H-imidazole-1-carboxylate (1 equiv.) was added. The mixture stirred for 1 h at −78° C. followed by the addiction of acrylonitrile (1.5 equiv.). The mixture was allowed to warm to room temperature across 2 h. It was then diluted with ethyl acetate and washed with 1 M HCl solution, brine, and then dried over sodium sulfate. The mixture was then concentrated and the crude material was purified on silica to provide tert-butyl 2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-1H-imidazole-1-carboxylate see for example PCT Int. Appl., 2015005901, 15 Jan. 2015.

Ethyl 3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7-(2-cyanoethyl)-5-oxo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-7-carboxylate

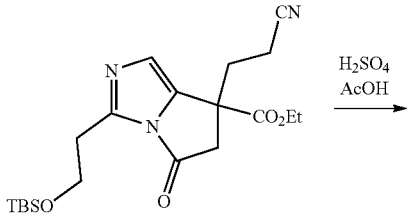




tert-Butyl-2-(2-((tert-butyldimethyl silyl)oxy)ethyl)-5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-1H-imidazole-1-carboxylate is dissolved in dichloromethane and cooled to 0° C. Trifluoroacetic acid (10 equiv.) is added and the mixture is allowed to stir. After 3 hours, the reaction is quenched with saturated sodium bicarbonate solution and diluted with dichloromethane. The aqueous layer is separated and extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The free pyrazole (1 equiv.) is then dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is then purified on silica providing ethyl 3-(2-((tert-butyldimethyl silyl)oxy)ethyl)-7-(2-cyanoethyl)-5-oxo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-7-carboxylate.

3'-(2-Hydroxyethyl)spiro[piperidine-3,7'-pyrrolo[1,2-c]imidazole]-2,5',6(6'H)-trione



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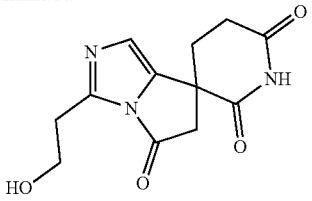
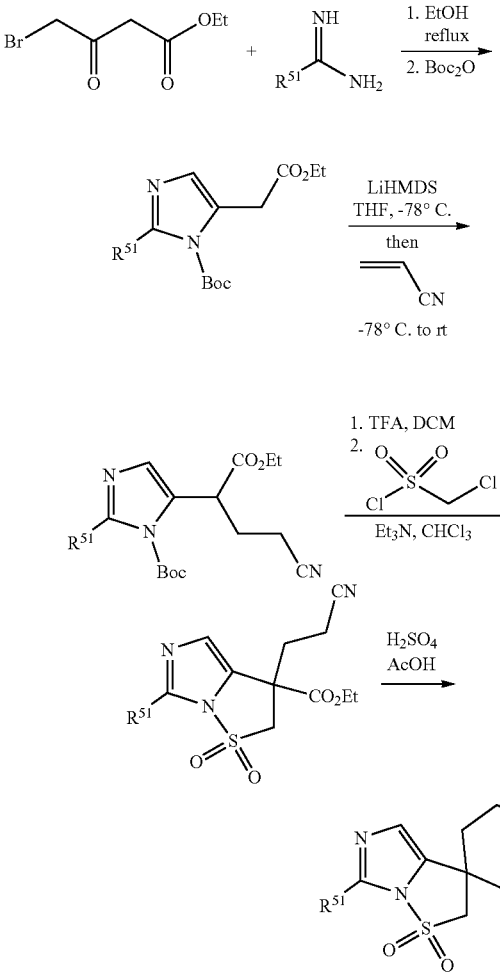


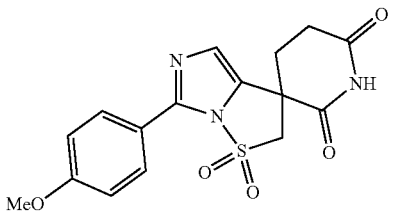
Ethyl-3-(2-((tert-butyldimethyl silyl)oxy)ethyl)-7-(2-cyanoethyl)-5-oxo-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-7-carboxylate is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is then heated at reflux for 2 hours. The mixture is then cooled to room temperature, extracted with ethyl acetate, and the organic layer was separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 3'-(2-hydroxyethyl)spiro[piperidine-3,7'-pyrrolo[1,2-c]imidazole]-2,5',6(6'H)-trione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme

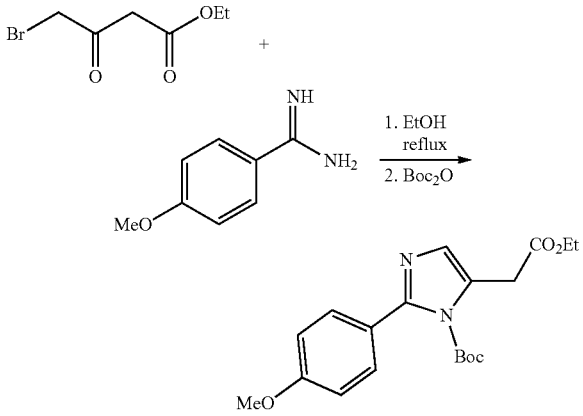


R^{51} is independently selected from H, Alkyl, Aryl, HetAryl

Representative Synthesis 17: 6-(4-Methoxyphenyl)-2H-spiro[imidazo[1,5-b]isothiazole-3,3'-piperidine]-2',6'-dione 1,1-dioxide



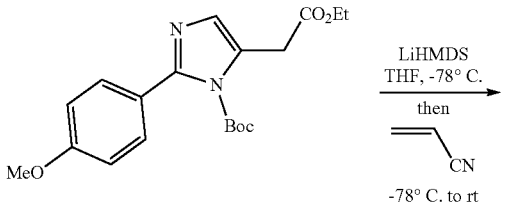
tert-Butyl 5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate



Ethyl 4-bromo-3-oxobutanoate (1 equiv.) and 4-methoxybenzimidamide (1 equiv.) are dissolved in ethanol. The mixture is heated to reflux and allowed to stir for 12 hours. It is then cooled to room temperature and concentrated under vacuum see for example *Journal of Medicinal Chemistry*, 2014, 57(12), 5293-5305.

The resulting residue is dissolved in THF. DMAP (0.1 equiv.), Hunig's base (1.5 equiv.) and Boc_2O (1.2 equiv.) are added and the reaction is allowed to stir at room temperature for 24 h. Water is then added and the mixture is diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating. The crude material is then purified on silica providing tert-butyl 5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate.

tert-Butyl 5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate



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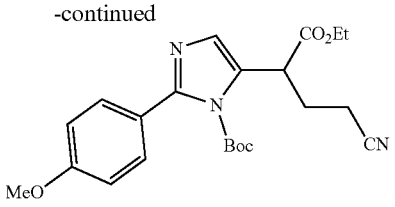
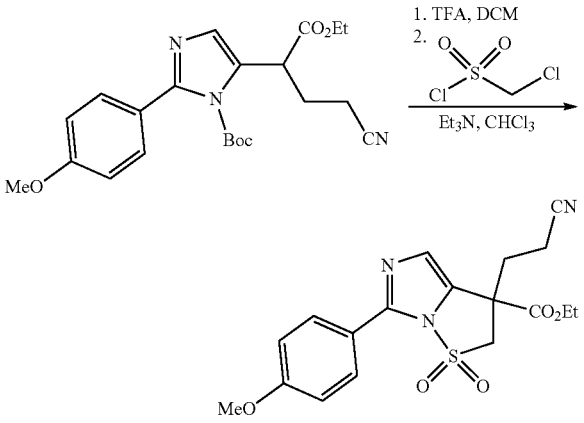


To a solution of diisopropylethylamine (1.6 equiv.) in tetrahydrofuran was added n-butyllithium (1.5 equiv.) at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and then cooled to −78° C. Hexamethylphosphorictriamide (1.1 equiv.) was then added. The solution was allowed to stir for 15 minutes before the addition of a tetrahydrofuran solution of tert-butyl 5-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate (1 equiv.) was added. The mixture stirred for 1 h at −78° C. followed by the addiction of acrylonitrile (1.5 equiv.). The mixture was allowed to warm to room temperature across 2 h. It was then diluted with ethyl acetate and washed with 1 M HCl solution, brine, and then dried over sodium sulfate. The mixture was then concentrated and the crude material was purified on silica to provide tert-butyl 5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate see for example PCT Int. Appl., 2015005901, 15 Jan. 2015.

Ethyl 3-(2-cyanoethyl)-6-(4-methoxyphenyl)-2,3-dihydroimidazo[1,5-b]isothiazole-3-carboxylate 1,1-dioxide

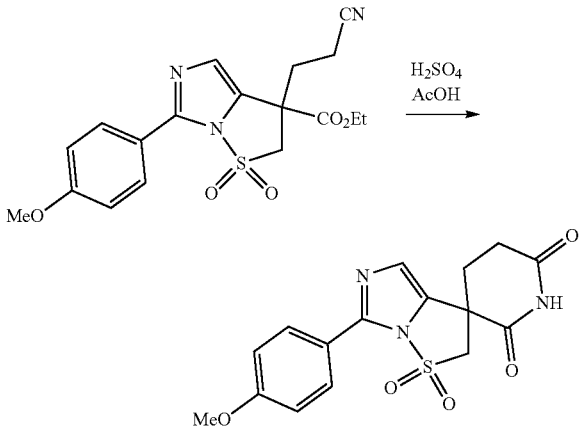


tert-Butyl-5-(4-cyano-1-ethoxy-1-oxobutan-2-yl)-2-(4-methoxyphenyl)-1H-imidazole-1-carboxylate is dissolved in dichloromethane and cooled to 0° C. Trifluoroacetic acid (10 equiv.) is added and the mixture is allowed to stir. After 3 hours, the reaction is quenched with saturated sodium bicarbonate solution and diluted with dichloromethane. The aqueous layer is separated and extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

The free pyrazole (1 equiv.) is then dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and chloromethanesulfonyl chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous

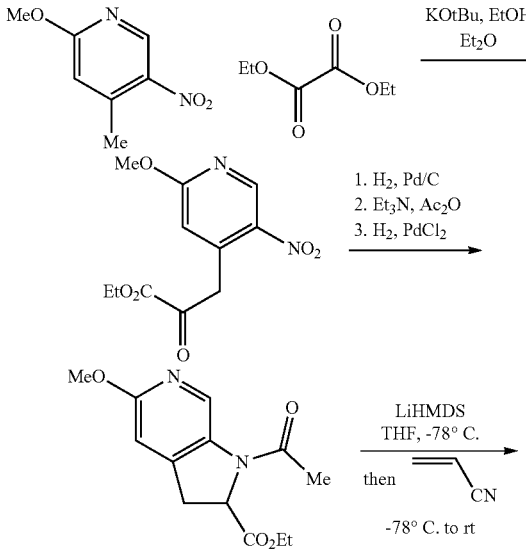
layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is then purified on silica providing ethyl 3-(2-cyanoethyl)-6-(4-methoxyphenyl)-2,3-dihydroimidazo[1,5-b]isothiazole-3-carboxylate 1,1-dioxide.

6-(4-Methoxyphenyl)-2H-spiro[imidazo[1,5-b]isothiazole-3,3'-piperidine]-2',6'-dione 1,1-dioxide



Ethyl-3-(2-cyanoethyl)-6-(4-methoxyphenyl)-2,3-dihydroimidazo[1,5-b]isothiazazole-3-carboxylate 1,1-dioxide is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is then heated at reflux for 2 hours. The mixture is then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 6-(4-methoxyphenyl)-2H-spiro[imidazo[1,5-b]isothiazole-3,3'-piperidine]-2',6'-dione 1,1-dioxide see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme:



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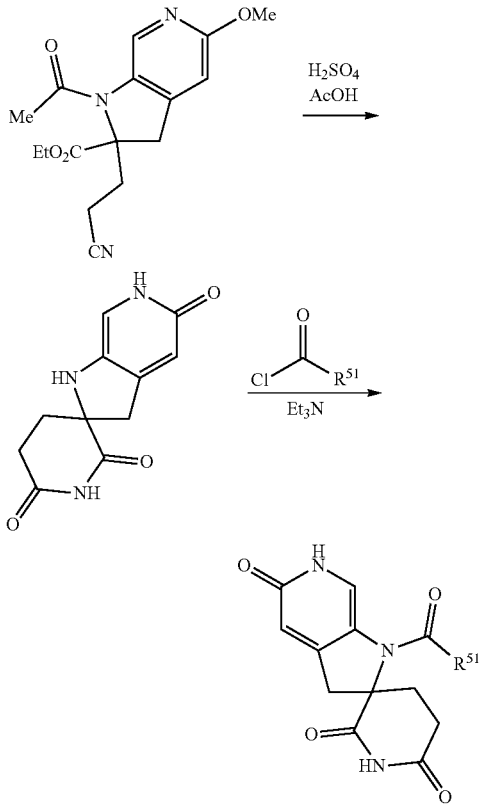
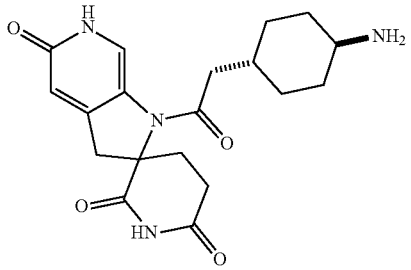
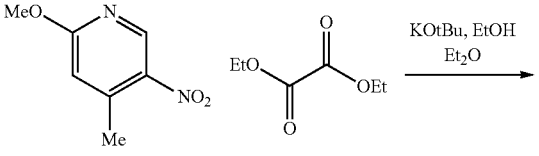


R^{51} is independently selected from Alkyl, Aryl, HetAryl

Representative Synthesis 18: 1'-(2-((1r,4r)-4-Aminocyclohexyl)acetyl)-1',6'-dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c]pyridine]-2,5',6(3'H)-trione



Ethyl 3-(2-methoxy-5-nitropyridin-4-yl)-2-oxopropanoate



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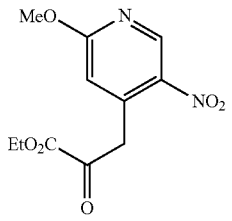
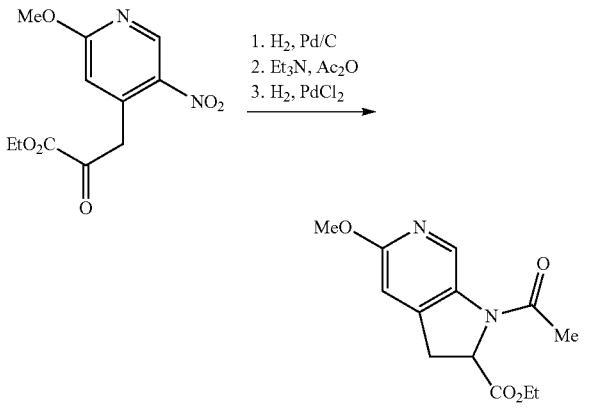


Potassium tert-butoxide (1 equiv.) is dissolved in a mixture of 10:1 mixture of diethyl ether and ethanol. 2-methoxy-4-methyl-5-nitropyridine (1 equiv.) is added. After 15 minutes, diethyl oxalate (1 equiv.) is added dropwise. The mixture is allowed to stir for 12 hours. The precipitate obtained is filtered off and rinsed with diethyl ether and then diluted with a large volume of water. Glacial acetic acid is added until a pH of 4 is obtained. The reaction mixture is then stirred at room temperature for 2 hours and then filtered to yield ethyl 3-(2-methoxy-5-nitropyridin-4-yl)-2-oxopropanoate see for example PCT Int. Appl., 2010007248, 21 Jan. 2010.

Ethyl-1-acetyl-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c] pyridine-2-carboxylate

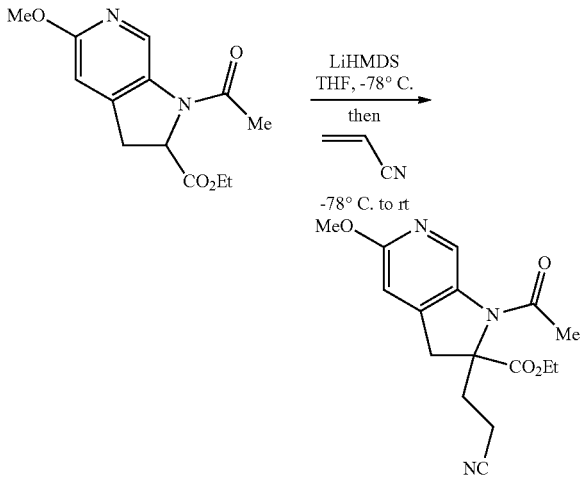


Ethyl-3-(2-methoxy-5-nitropyridin-4-yl)-2-oxopropanoate is dissolved in ethanol. Palladium on carbon (20% by weight) is added. Hydrogen gas is bubbled through the reaction mixture for 24 h. The reaction is then filtered through a pad of celite and concentrated. The residue obtained is dissolved in a 1:1 mixture of diethyl ether and water. The organic layer is separated and the aqueous layer is extracted with diethyl ether. The organic phases are combined and washed with brine before drying over sodium sulfate and concentrating.

The resulting aniline (1 equiv.) is then dissolved in dichloromethane. Triethylamine (2 equiv.) and 4-dimethylaminopyridine (0.1 equiv.) are added followed by the dropwise addition of acetic anhydride (1.1 equiv.). The mixture is allowed to stir for 24 h at room temperature. The reaction mixture is then diluted with water. The aqueous layer is separated and extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating.

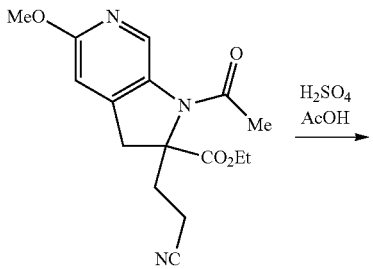
The crude product (1 equiv.) is then dissolved in ethanol. Palladium(II) chloride (0.2 equiv.) is added and hydrogen gas is bubbled through the reaction mixture for 24 h. The reaction vessel is then purged of hydrogen and the mixture is filtered through a pad of celite and concentrated. The resulting material is then purified on silica to afford ethyl 1-acetyl-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate see for example PCT Int. Appl., 2010007248, 21 Jan. 2010.

Ethyl-1-acetyl-2-(2-cyanoethyl)-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



To a solution of diisopropylethylamine (1.6 equiv.) in tetrahydrofuran was added n-butyllithium (1.5 equiv.) at 0° C. The reaction mixture was stirred at 0° C. for 30 minutes and then cooled to −78° C. Hexamethylphosphorictriamide (1.1 equiv.) was then added. The solution was allowed to stir for 15 minutes before the addition of a tetrahydrofuran solution of ethyl 1-acetyl-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (1 equiv.) was added. The mixture stirred for 1 h at −78° C. followed by the addiction of acrylonitrile (1.5 equiv.). The mixture was allowed to warm to room temperature across 2 h. It was then diluted with ethyl acetate and washed with 1 M HCl solution, brine, and then dried over sodium sulfate. The mixture was then concentrated and the crude material was purified on silica to provide ethyl 1-acetyl-2-(2-cyanoethyl)-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate see for example PCT Int. Appl., 2015005901, 15 Jan. 2015.

1',6'-Dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c] pyridine]-2,5',6(3'H)-trione



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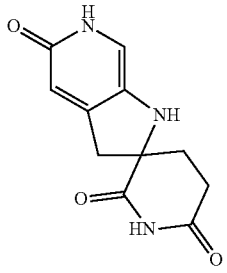
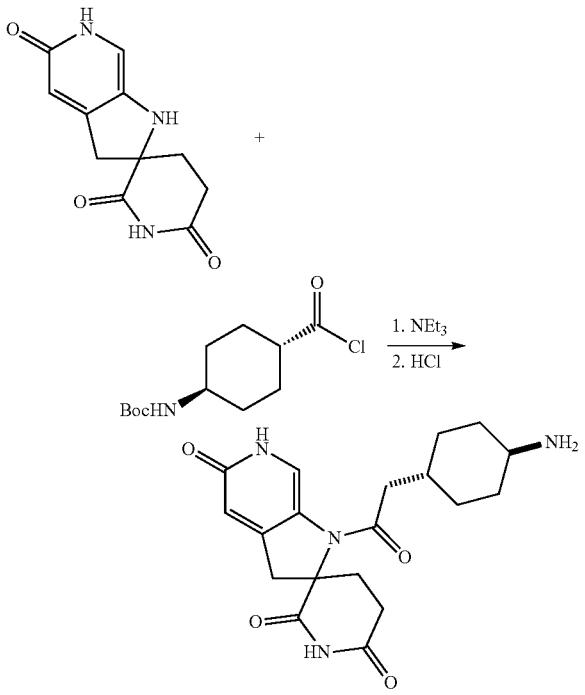


Ethyl-1-acetyl-2-(2-cyanoethyl)-5-methoxy-2,3-dihydro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is then heated at reflux for 2 hours. The mixture is then cooled to room temperature and extracted with ethyl acetate and the organic layer was separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 1',6'-dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c]pyridine]-2,5',6(3'H)-trione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

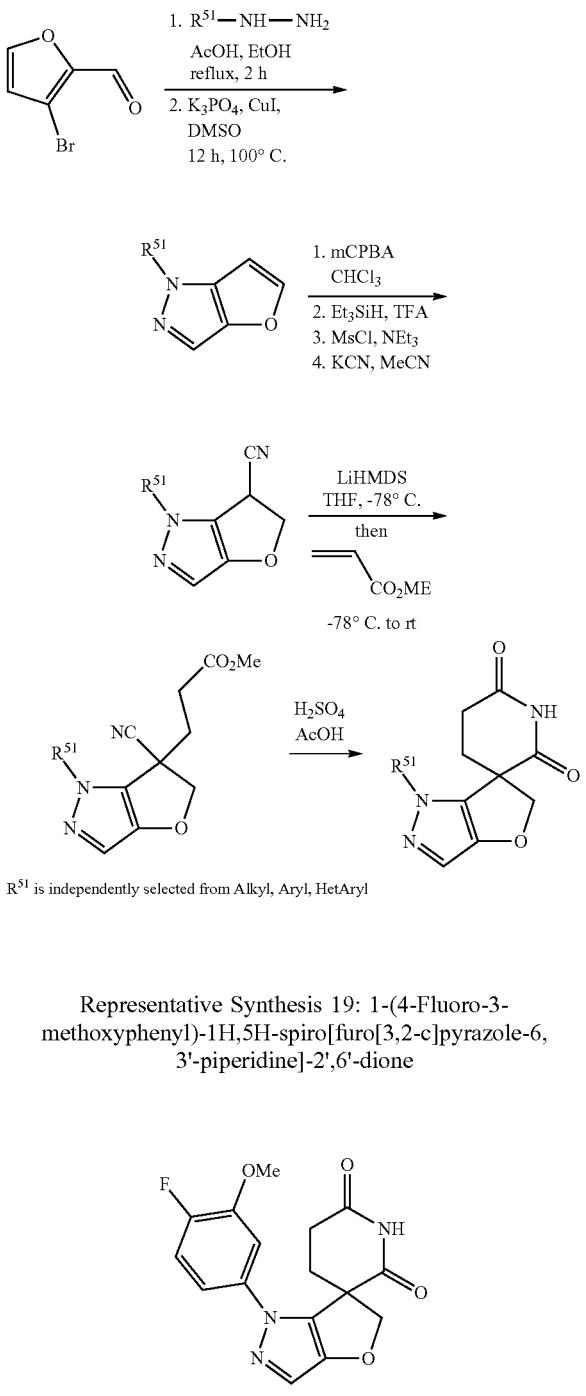
1'-(2-((1r,4r)-4-Aminocyclohexyl)acetyl)-1',6'-dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c]pyridine]-2,5',6(3'H)-trione



1',6'-Dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c]pyridine]-2,5',6(3'H)-trione (1 equiv.) is dissolved in DCM. Triethylamine (2 equiv.) is added along with DMAP (0.2 equiv.). The mixture is then cooled to 0° C. and the acid chloride (1.1 equiv.) is added. After stirring overnight, the mixture is quenched with 1.0 M HCl aqueous solution. The organic layer is separated and the aqueous layer is extracted with DCM (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure.

The crude product is then taken up in dioxane. HCl in dioxane (4.0 M, 10 equiv.) is added and the mixture is allowed to stir overnight. The solvent is then evaporated and the crude residue is purified on silica to provide 1'-(2-((1r,4r)-4-aminocyclohexyl)acetyl)-1',6'-dihydrospiro[piperidine-3,2'-pyrrolo[2,3-c]pyridine]-2,5',6(3'H)-trione.

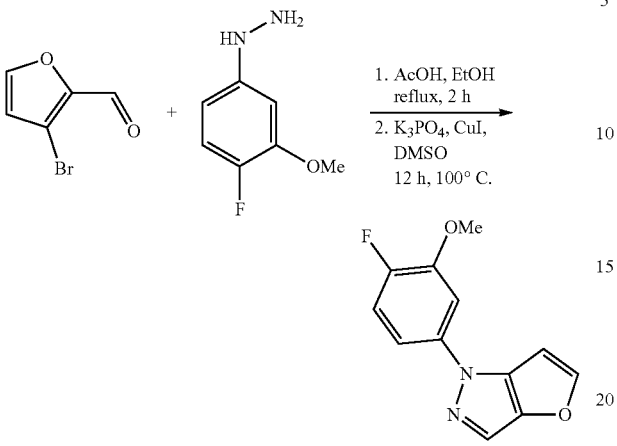
General Scheme



R^{51} is independently selected from Alkyl, Aryl, HetAryl

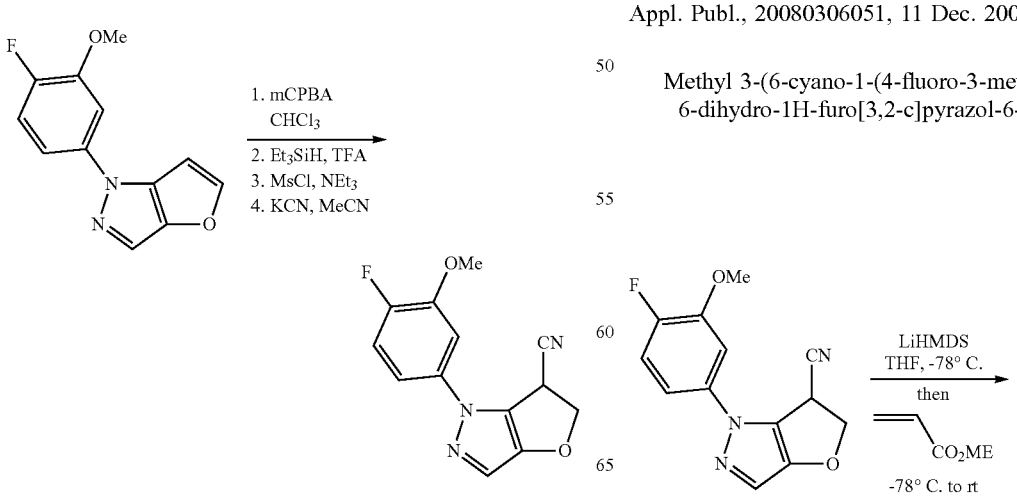
Representative Synthesis 19: 1-(4-Fluoro-3-methoxyphenyl)-1H,5H-spiro[furo[3,2-c]pyrazole-6,3'-piperidine]-2',6'-dione

1-(4-Fluoro-3-methoxyphenyl)-1H-furo[3,2-c]pyrazole



3-Bromofuran-2-carbaldehyde (1 equiv.) is dissolved in acetic acid. This solution is added to a solution of (4-fluoro-3-methoxyphenyl)hydrazine (1 equiv.) in ethanol. The solution is then heated to reflux. After the starting material is judged to be consumed by TLC, the reaction is then cooled to room temperature and the solvent is evaporated, yielding the desired crude hydrazone. The crude hydrazone (1 equiv.) is then dissolved in DMSO. Tribasic potassium phosphate (2 equiv.) is added followed by copper iodide (1 equiv.). The mixture is heated to 100° C. for 12 hours. The mixture was then cooled to room temperature and then diluted with ice water. Concentrated aqueous ammonia solution is then added and the mixture is allowed to stir for 15 minutes. After 15 minutes, the solids were extracted and the residue was dissolved in ethyl acetate. The organic layer was washed with water and dried over sodium sulfate before concentrating. The resulting material was purified on silica to provide 1-(4-fluoro-3-methoxyphenyl)-1H-furo[3,2-c]pyrazole see for example *Chinese Journal of Chemistry,* 2011, 29(6), 1199-1204.

1-(4-Fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c] pyrazole-6-carbonitrile



1-(4-Fluoro-3-methoxyphenyl)-1H-furo[3,2-c]pyrazole (1 equiv.) was dissolved in dichloromethane and cooled to 0° C. m-Chloroperbenzoic acid (1.2 equiv.) was added portionwise and the mixture was allowed to stir for 2 hours. It was then quenched with 0.5 M sodium thiosulfate solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The organic layer was then washed with brine and dried over sodium sulfate before concentrating under reduced pressure affording the desired epoxide.

The epoxide (1 equiv.) was dissolved in dichloromethane. Triethylsilane (10 equiv.) was added followed by catalytic trifluoroacetic acid. The mixture was allowed to stir at room temperature until the starting material had been consumed as judged by TLC and LCMS. The mixture was then quenched with saturated sodium bicarbonate aqueous solution. The aqueous layer was separated and extracted with dichloromethane (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating. The resulting material was purified on silica to provide 1-(4-fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c] pyrazol-6-ol.

1-(4-Fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazol-6-ol (1 equiv.) was then dissolved in dichloromethane at 0° C. Hunig's base (2 equiv.) was then added followed by mesyl chloride (1 equiv.). The solution was allowed to warm to room temperature and stir for 2 hours. The mixture was then quenched with saturated sodium bicarbonate aqueous solution. The aqueous layer was separated and extracted with dichloromethane (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating. The resulting material was purified on silica to provide the desired mesylated alcohol.

1-(4-Fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazol-6-yl methanesulfonate (1 equiv.) was then dissolved in acetonitrile. Potassium cyanide (3 equiv.) was added and the mixture was heated to 80° C. for 16 h. The reaction mixture was then cooled to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried and filtered. The material was then concentrated and the purified on silica to provide 1-(4-fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazole-6-carbonitrile see for example U.S. Pat. Appl. Publ., 20080306051, 11 Dec. 2008.

Methyl 3-(6-cyano-1-(4-fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazol-6-yl)propanoate

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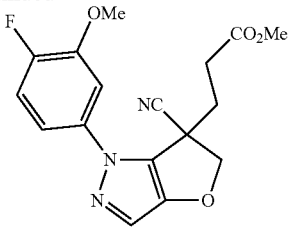
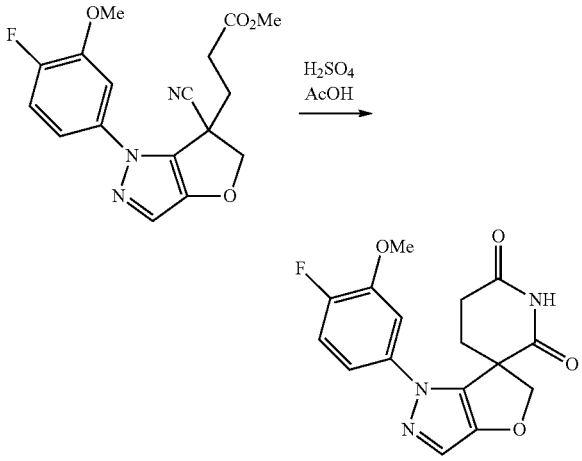


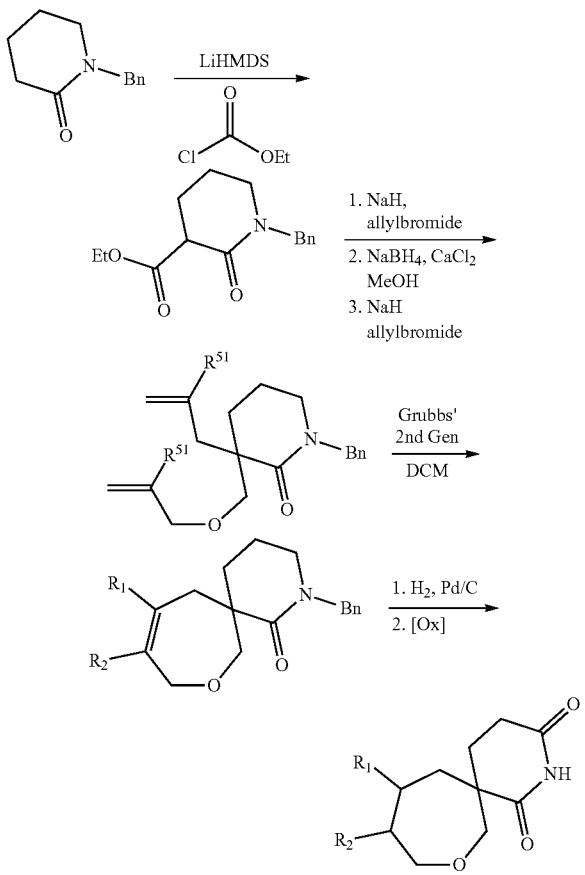
1-(4-Fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazole-6-carbonitrile (1 equiv.) is dissolved in dry THF and cooled to −78° C. A solution of LiHMDS (1.0 M in THF) (1.1 equiv.) is then added dropwise and the solution is stirred for 1 hour. Methyl acrylate (1 equiv.) was then added dropwise. The is allowed to stir for 30 minutes and is then warmed gradually to room temperature. When the reaction is judged to be complete based on TLC or LCMS analysis, it is quenched with saturated aqueous ammonium chloride solution and diluted with ethyl acetate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude product is then purified on silica providing methyl 3-(6-cyano-1-(4-fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazol-6-yl) propanoate.

1-(4-Fluoro-3-methoxyphenyl)-1H,5H-spiro[furo[3,2-c]pyrazole-6,3'-piperidine]-2',6'-dione



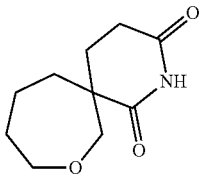
Methyl-3-(6-cyano-1-(4-fluoro-3-methoxyphenyl)-5,6-dihydro-1H-furo[3,2-c]pyrazol-6-yl)propanoate is dissolved in a 10:1 mixture of acetic acid and concentrated sulfuric acid. The resulting mixture is heated to reflux for 2 hours. Water is then added to the reaction mixture which is heated at reflux for 2 hours. The mixture is then cooled to room temperature and extracted with ethyl acetate and the organic layer is separated. The organic layer is then washed with brine and dried over sodium sulfate before concentrating to afford 1-(4-fluoro-3-methoxyphenyl)-1H,5H-spiro[furo[3,2-c]pyrazole-6,3'-piperidine]-2',6'-dione see for example PCT Int. Appl., 2009157515, 30 Dec. 2009.

General Scheme:

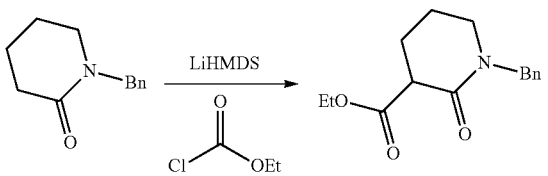


R^{51} is independently selected from H, Alkyl, Aryl, HetAryl

Representative Synthesis 20:
8-Oxa-2-azaspiro[5.6]dodecane-1,3-dione



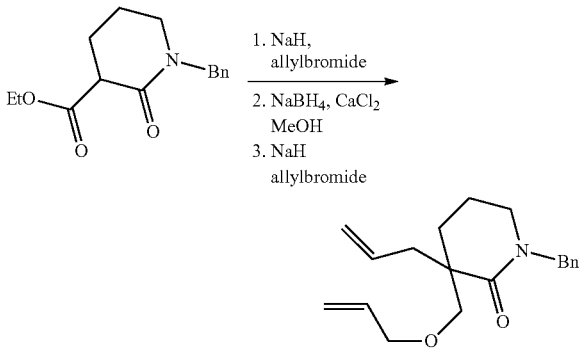
Ethyl 1-benzyl-2-oxopiperidine-3-carboxylate



1-Benzylpiperidin-2-one (1 equiv.) was dissolved in toluene and cooled to 0° C. Freshly prepared LiHMDS (2.1

equiv.) is added slowly and allowed to stir for 15 minutes. Ethyl chloroformate (1 equiv.) is then added slowly and the mixture is allowed to stir for 30 minutes. The reaction is then quenched with saturated ammonium chloride aqueous solution and diluted with ethyl acetate. The aqueous layer is separated and extracted with ethyl acetate (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating under reduced pressure. The crude material is then purified on silica to afford ethyl 1-benzyl-2-oxopiperidine-3-carboxylate see for example *Synlett,* 2016, 27(7), 1056-1060.

3-Allyl-3-((allyloxy)methyl)-1-benzylpiperidin-2-one

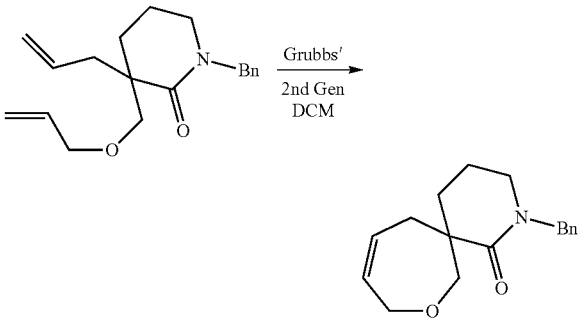


Ethyl 1-benzyl-2-oxopiperidine-3-carboxylate (1 equiv.) is dissolved in N,N-dimethylformamide and cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.5 equiv.) is added and the mixture is allowed to stir for 20 minutes. Allylbromide (3 equiv.) was then added dropwise. The reaction was allowed to warm to room temperature and stir for 12 hours. It was then quenched with saturated ammonium chloride aqueous solution and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating. The crude material was purified on silica to provide the desired allylated product see for example *Organic Letters,* 2009, 11(19), 4370-4373.

Ethyl 3-allyl-1-benzyl-2-oxopiperidine-3-carboxylate (1 equiv.) and calcium (II) chloride (1 equiv.) are suspended in methanol and cooled to 0° C. Sodium borohydride (2 equiv.) are added and the mixture is allowed to warm to room temperature and stir for 12 hours. The mixture is then quenched with 3 N citric acid solution until the mixture is completely soluble with a pH of 4. The mixture is diluted with dichloromethane and the aqueous layer is separated and extracted with dichloromethane (3×). The combined organic layers are washed with brine and dried over sodium sulfate before concentrating to provide 3-allyl-1-benzyl-3-(hydroxymethyl)piperidin-2-one see for example *European Journal of Organic Chemistry,* 2007, 14, 2365-2371.

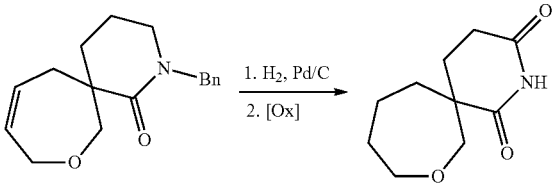
3-Allyl-1-benzyl-3-(hydroxymethyl)piperidin-2-one (1 equiv.) is then dissolved in N,N-dimethylformamide and cooled to 0° C. Sodium hydride (60% dispersion in mineral oil, 1.5 equiv.) is added and the mixture is allowed to stir for 20 minutes. Allylbromide (3 equiv.) was then added dropwise. The reaction was allowed to warm to room temperature and stir for 12 hours. It was then quenched with saturated ammonium chloride aqueous solution and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate before concentrating. The crude material was purified on silica to provide 3-allyl-3-((allyloxy)methyl)-1-benzylpiperidin-2-one.

2-Benzyl-8-oxa-2-azaspiro[5.6]dodec-10-en-1-one



To a solution of 3-allyl-3-((allyloxy)methyl)-1-benzylpiperidin-2-one (1 equiv.) in n-hexane was added 2nd generation Grubbs catalyst (0.05 equiv.) in n-hexane at room temperature under Ar gas. The mixture was warmed to 55° C. and stirred at this temperature for 6h. The solution was cooled to room temperature and concentrated. The residue was then purified on silica providing 2-benzyl-8-oxa-2-azaspiro[5.6]dodec-10-en-1-one see for example *Journal of the American Chemical Society,* 2015, 137(49), 15346-15349.

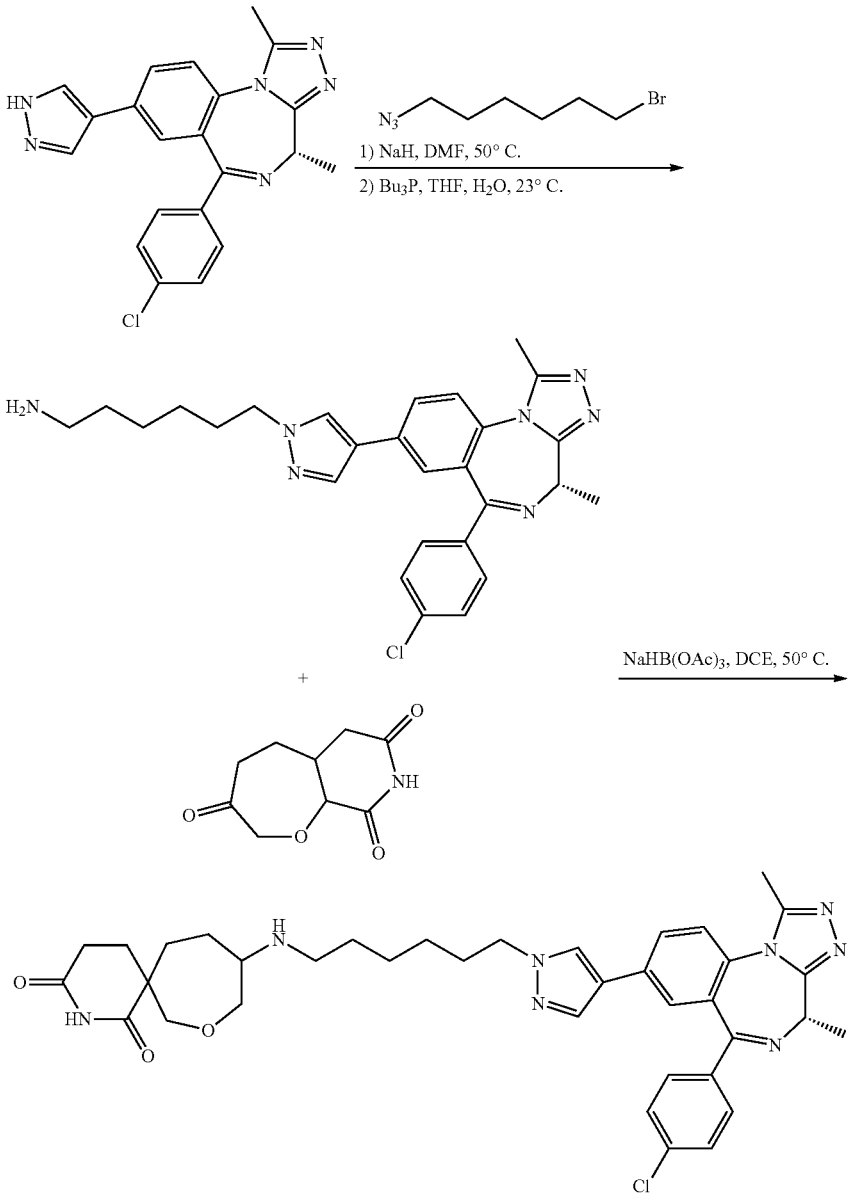
8-Oxa-2-azaspiro[5.6]dodecane-1,3-dione



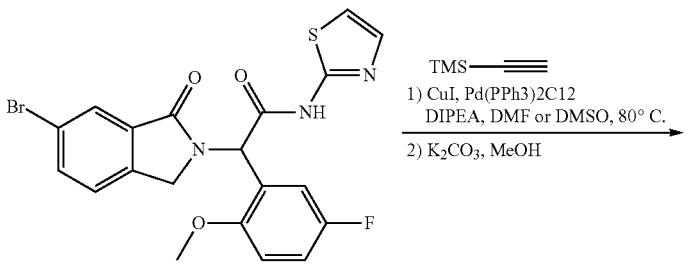
2-Benzyl-8-oxa-2-azaspiro[5.6]dodec-10-en-1-one (1 equiv.) is dissolved in ethanol. Palladium on carbon (20% by weight) is added. Hydrogen gas is bubbled through the reaction mixture for 24 h. The reaction is then filtered through a pad of celite and concentrated. The residue obtained is dissolved in a 1:1 mixture of diethyl ether and water. The organic layer is separated and the aqueous layer is extracted with diethyl ether. The organic phases are combined and washed with brine before drying over sodium sulfate and concentrating. 8-oxa-2-azaspiro[5.6]dodecan-1-one (1 equiv.) is then dissolved in a 5:1 mixture of ethyl acetate and 1,2-dichloroethane. This mixture is added dropwise into a 10% aqueous solution of sodium periodate (1 equiv.) and ruthenium (IV) oxide (0.5 equiv.). The reaction is refluxed for 1.5 h. A small amount of isopropanol is added and the suspension is filtered. The filtrate is extracted with ethyl acetate and the organic layer is washed with 0.5 M sodium thiosulfate aqueous solution, then brine, and then dried of sodium sulfate. The solvent is removed under reduced pressure and the crude material is purified on silica to afford 8-oxa-2-azaspiro[5.6]dodecane-1,3-dione see for example *Organic Letters,* 2011, 13(3), 470-473.

IX. Exemplary Methods for Linking Targeting Ligand and Degron Through a Linker

Linking Scheme 1



Linking Scheme 2



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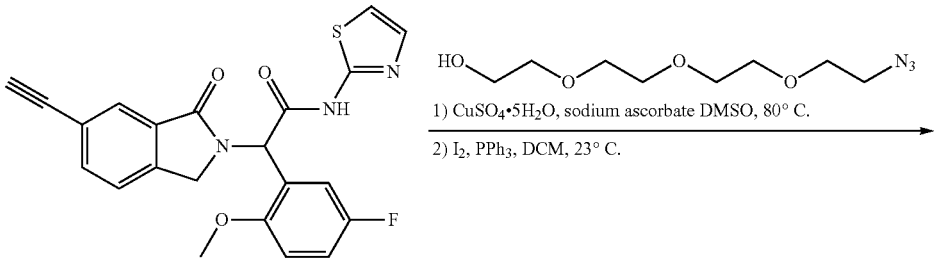
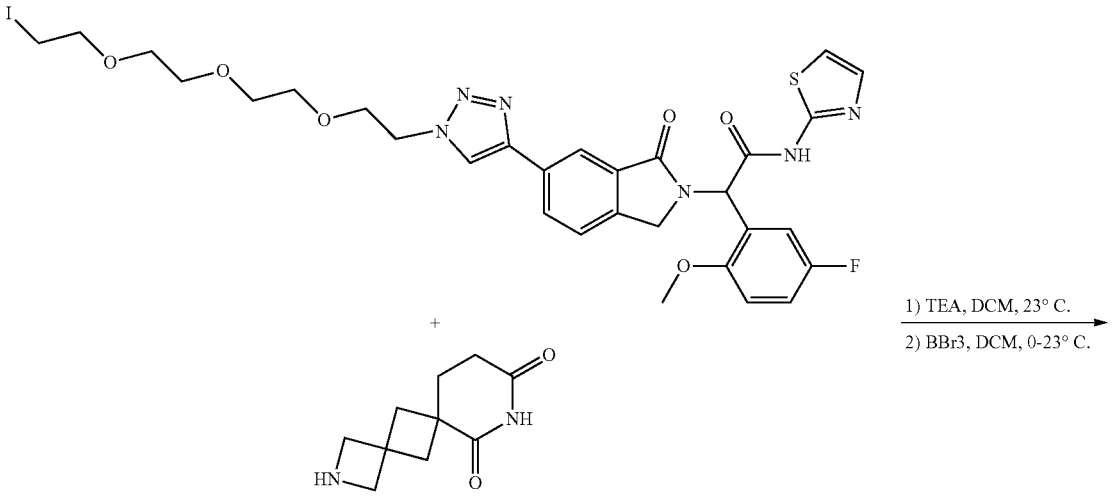
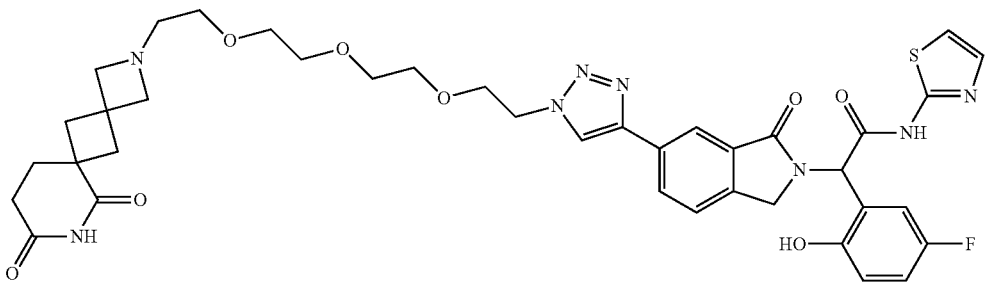

HO
N3
1) CuSO4•5H2O, sodium ascorbate DMSO, 80° C.
2) I2, PPh3, DCM, 23° C.


1) TEA, DCM, 23° C.
2) BBr3, DCM, 0-23° C.



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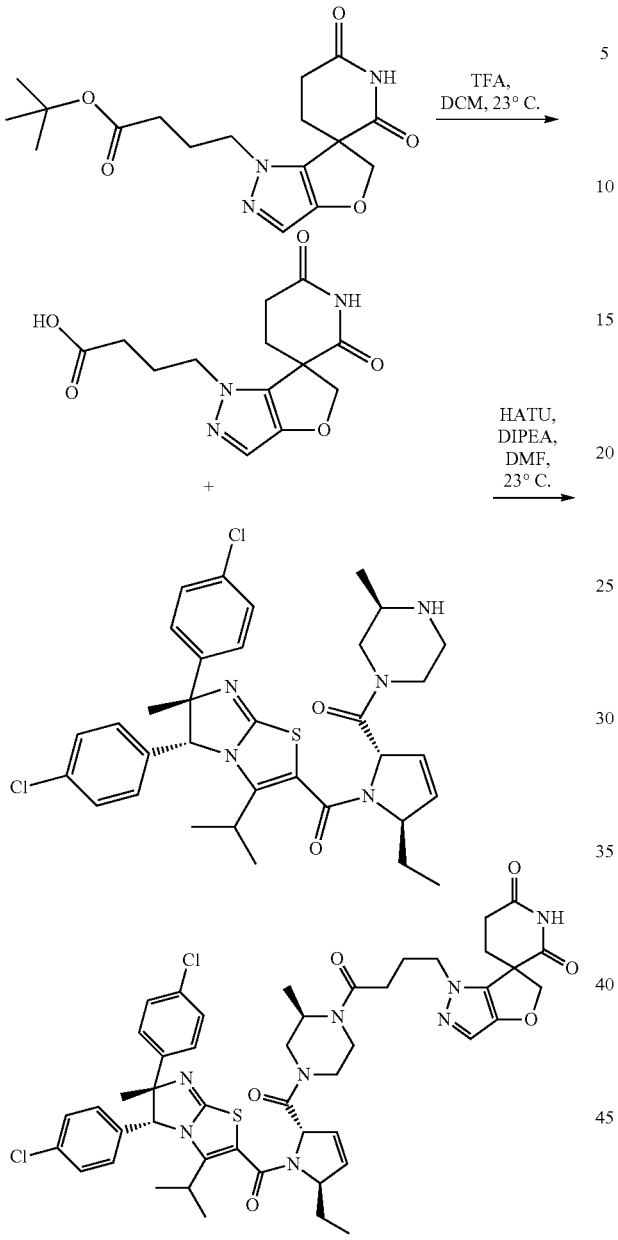
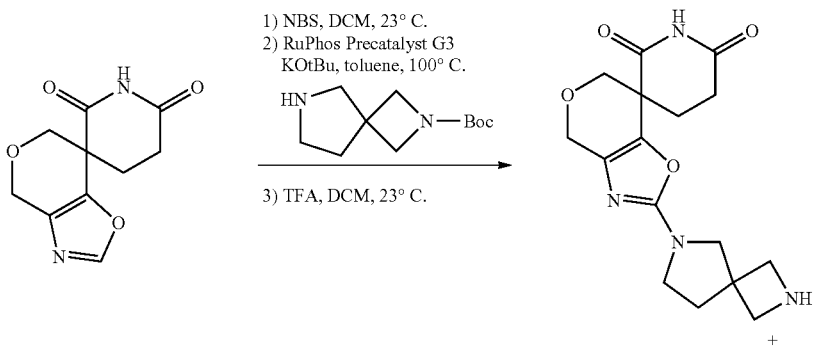


Linking Scheme 4



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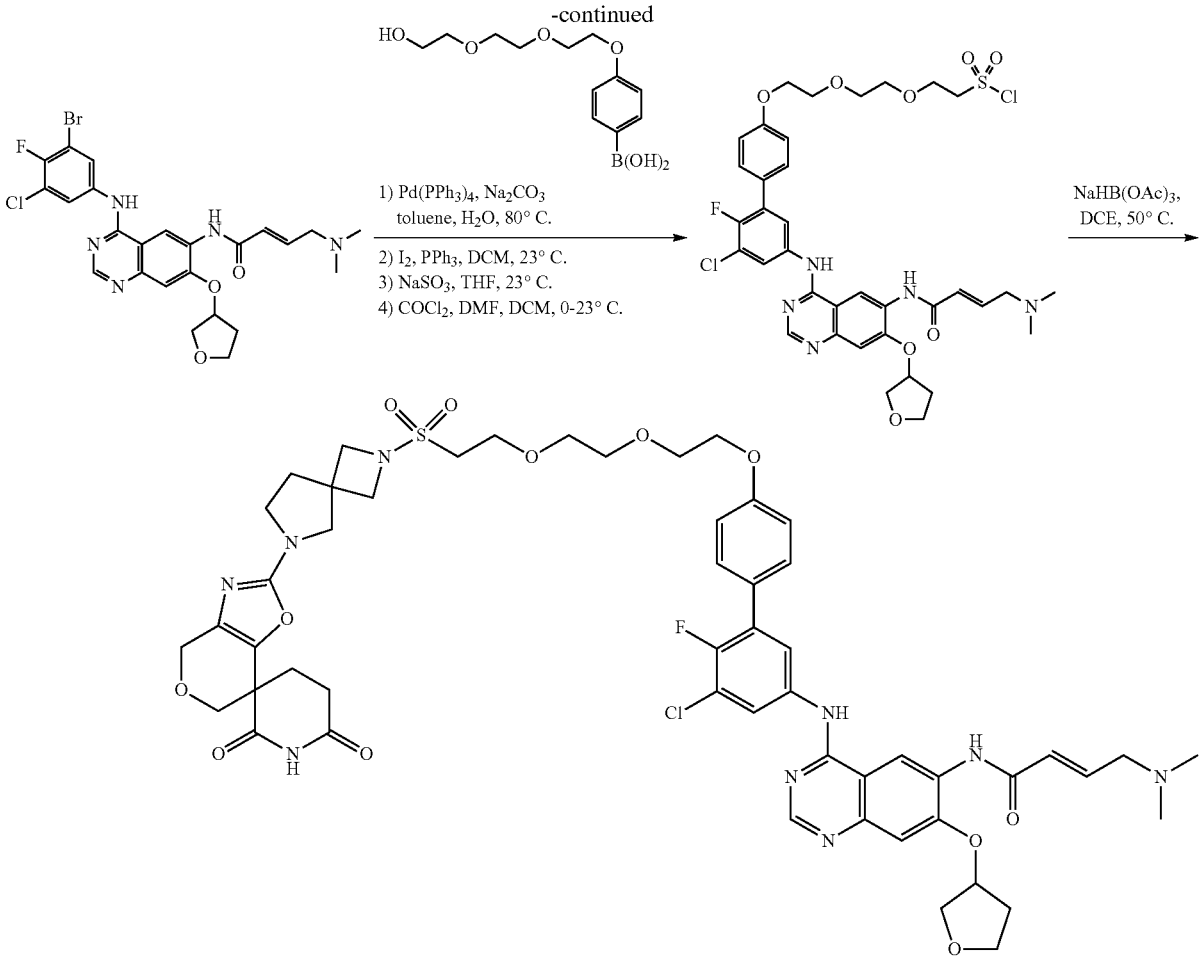
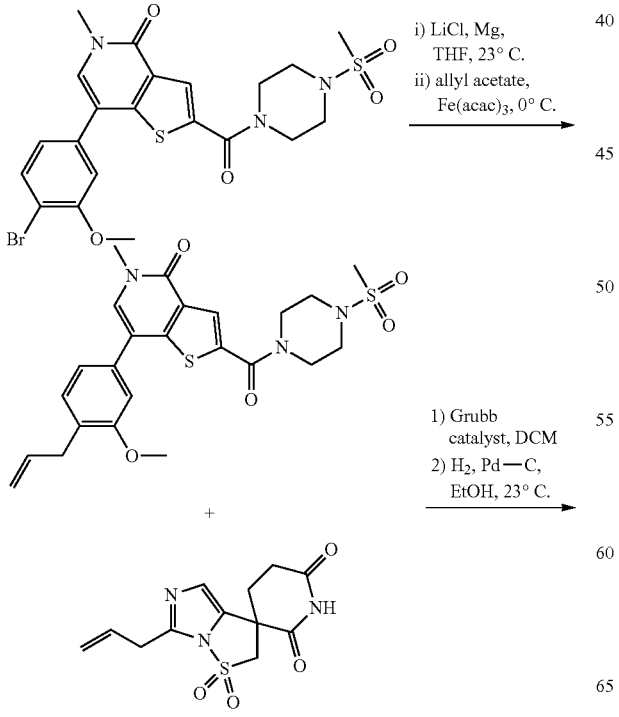


Linking Scheme 5



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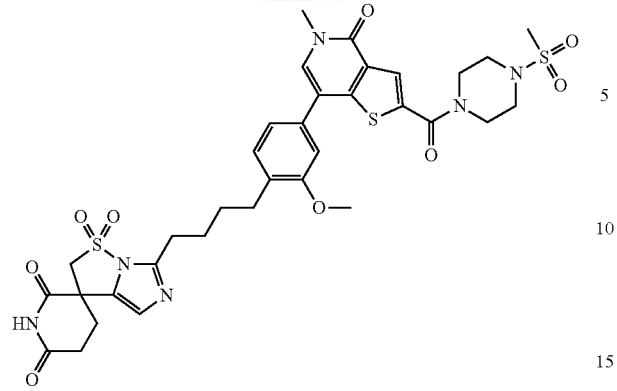
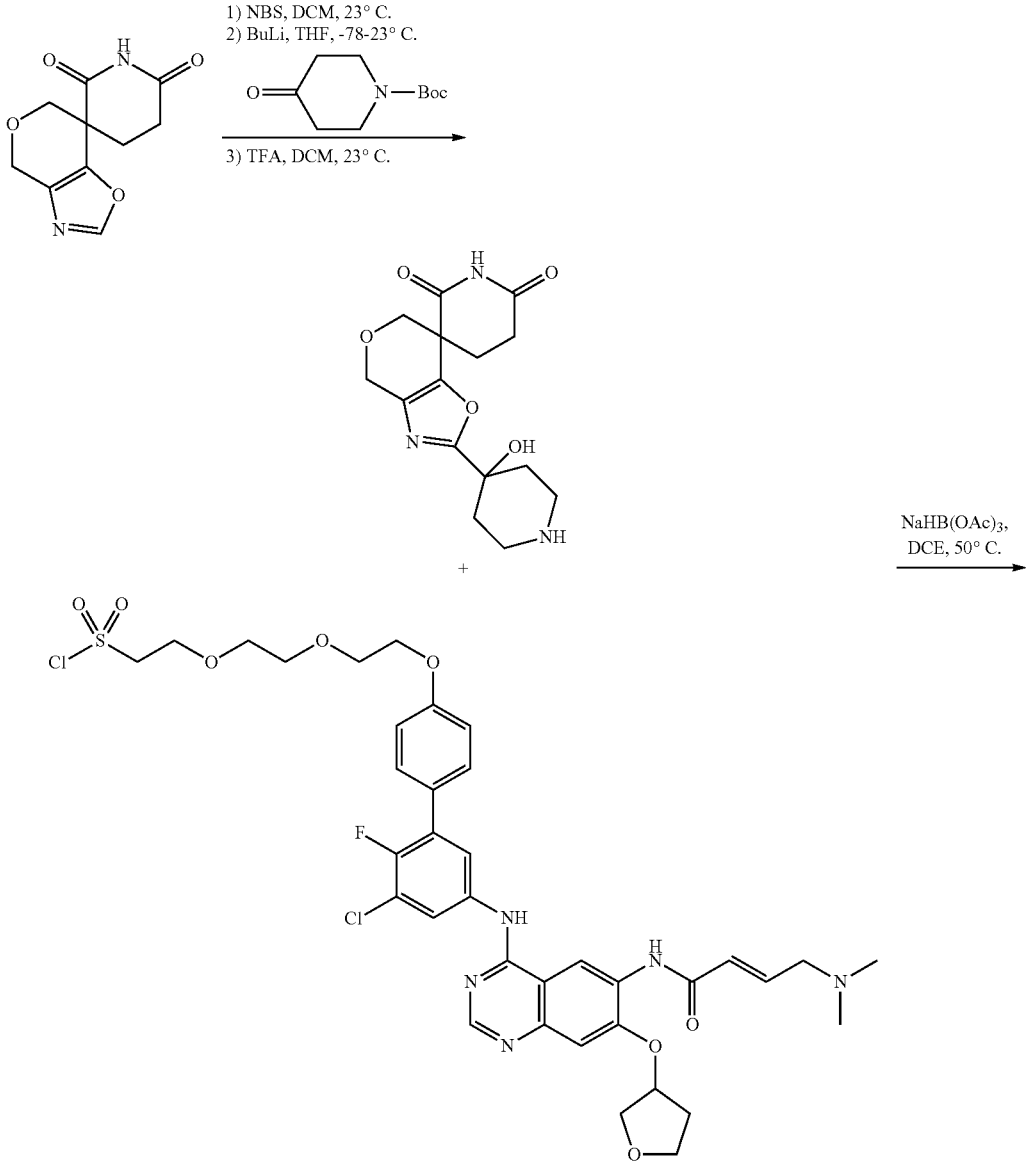


Linking Scheme 6



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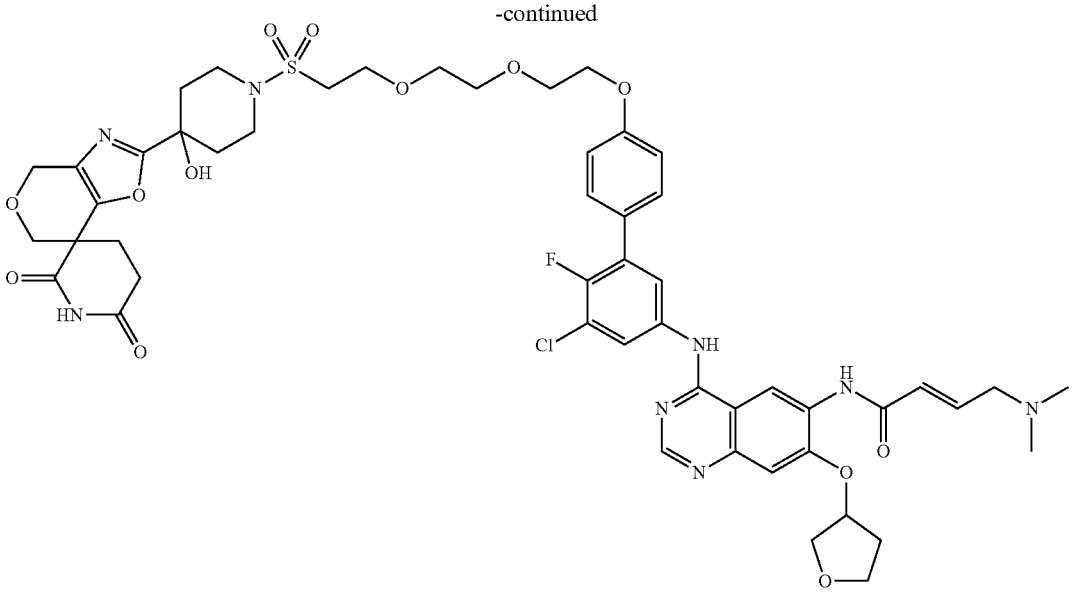
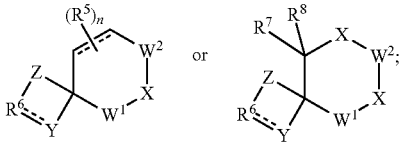


All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the invention as defined in the appended claims.

We claim:

1. A method for treating a human with a cancer mediated by a Targeted Protein selected from ABL, BRD4, BRD9, CBP, DOT1L, ERK1, ERK2, EZH2, FGFR3, FGFR4, FKBP, MDM2, NTRK1, PIK3CA, RET, WDR5, EGFR, bromodomain containing protein, glucocorticoid receptor, androgen receptor, and estrogen receptor, comprising administering an effective amount of a compound optionally in a pharmaceutically acceptable carrier, to a patient in need thereof, wherein the compound is of Formula:



or a pharmaceutically acceptable salt thereof;

wherein:

W^1 is C═O;

W^2 is C═O;

X is independently NH, NR^{12}, CH_2, CHR^{12}, $C(R^{12})_2$, O, or S;

n is 0, 1, 2, or 3;

═══ is a single or double bond;

Y and Z are each independently selected from the group consisting of CH_2, CHR^{12}, $C(R^{12})_2$, C(O), N, NH, NR^{13}, O, S, and S(O) as permitted by valency;

R^7 and R^8, are independently selected from the group consisting of hydrogen, alkyl, aliphatic, heteroaliphatic, aryl, heteroaryl, carbocyclic, hydroxyl, alkoxy, amine, —NHalkyl, and —$Nalkyl_2$;

or R^7 and R^8 form a 3-, 4-, 5-, or 6-membered spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O;

R^5 is selected at each instance from the group consisting of: alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, cyano, aryl, heteroaryl, heteroaliphatic, hetercyclic, —NHalkyl, —$N(alkyl)_2$, —$NHSO_2$alkyl, —$N(alkyl)SO_2$alkyl, —$NHSO_2$aryl, aliphatic, —$N(alkyl)SO_2$aryl, —$NHSO_2$alkenyl, —$N(alkyl)SO_2$alkenyl, —$NHSO_2$alkynyl, —$N(alkyl)SO_2$alkynyl, and haloalkyl;

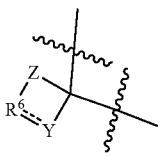
or two R^5 substituents together with the carbon atom(s) to which they are bound can form a 3, 4, 5 or 6 membered ring;

R^6 is a bond wherein Y or Z is substituted with R^{10};

or R^6 is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom wherein one of the ring atoms is substituted with R^{10} and the others are optionally substituted with R^{11};

wherein the contiguous atoms of R^6 can be attached through a single or double bond;

or



forms a bicyclic moiety which is substituted with R^{10} and optionally substituted with one or more groups independently selected from R^{11} and oxo;

R^{10} is Linker-Targeting Ligand;

R^{11} is selected at each instance from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aliphatic, heteroaliphatic, carbocyclic, halogen, hydroxyl, amino, cyano, alkoxy, aryl, heteroaryl, heterocyclic, carbocyclic, alkylamino, alkylhydroxyl, and haloalkyl;

R^{12} is selected from the group consisting of alkyl, alkene, alkyne, halogen, hydroxyl, alkoxy, azide, amino, —C(O)H, —C(O)OH, —C(O)(aliphatic), —C(O)O(aliphatic), —NH(aliphatic), —N(independently aliphatic)$_2$, —NHSO$_2$alkyl, —N(alkyl)SO$_2$alkyl, —NHSO$_2$aryl, —N(alkyl)SO$_2$aryl, —NHSO$_2$alkenyl, —N(alkyl)SO$_2$alkenyl, —NHSO$_2$alkynyl, —N(alkyl)SO$_2$alkynyl, aliphatic, heteroaliphatic, aryl, heteroaryl, heterocyclic, carbocyclic, cyano, nitro, nitroso, —SH, —Salkyl, and haloalkyl;

R^{13} is selected from the group consisting of alkyl, alkenyl, alkynyl, —C(O)H, —C(O)OH, —C(O)alkyl, and —C(O)Oalkyl;

Linker is a chemical group that covalently attaches the Degron to the Targeting Ligand;

and Targeting Ligand binds to the Targeted Protein.

2. The method of claim **1**, wherein X is NH.

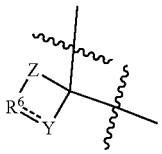
3. The method of claim **1**, wherein n is 0.

4. The method of claim **1**, wherein X is NH and n is 0.

5. The method of claim **1**, wherein R^7 and R^8 are hydrogen.

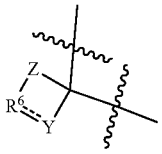
6. The method of claim **1**, wherein R^6 is a divalent moiety attached to Y and Z that contains 1 to 5 contiguous carbon atoms that form a 3 to 8-membered ring wherein 1, 2, or 3 carbon atoms can be replaced with a nitrogen, oxygen or sulfur atom wherein one of the ring atoms is substituted with R^{10} and the others are optionally substituted with R^{11}; wherein the contiguous atoms of R^6 can be attached through a single or double bond.

7. The method of claim **1**, wherein

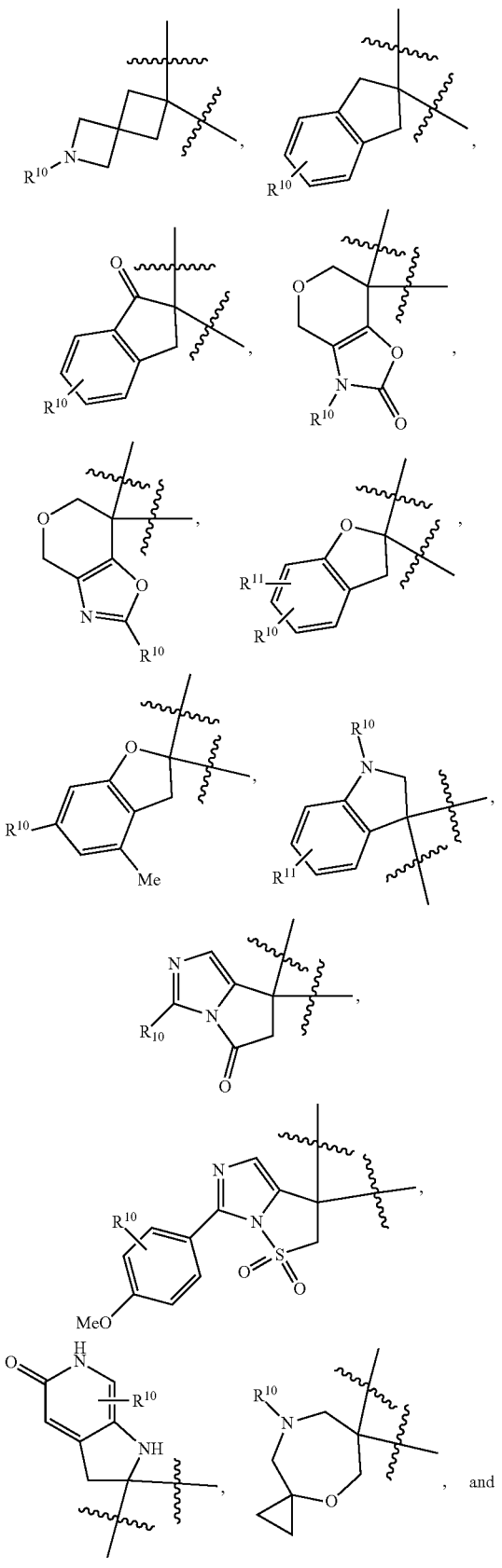


forms a bicyclic moiety which is substituted with R^{10} and optionally substituted with one or more groups independently selected from R^{11} and oxo.

8. The method of claim **1**, wherein



is selected from:



and

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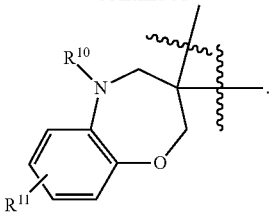


9. The method of claim 1, wherein the cancer is a solid tumor.

10. The method of claim 1, wherein the cancer is a hematological cancer.

11. The method of claim 1, wherein the cancer is multiple myeloma.

12. The method of claim 1, wherein the cancer is leukemia.

13. The method of claim 1, wherein the cancer is T-cell lineage acute lymphoblastic leukemia.

14. The method of claim 1, wherein the cancer is large granular lymphocytic leukemia.

15. The method of claim 1, wherein the cancer is Hodgkin's lymphoma.

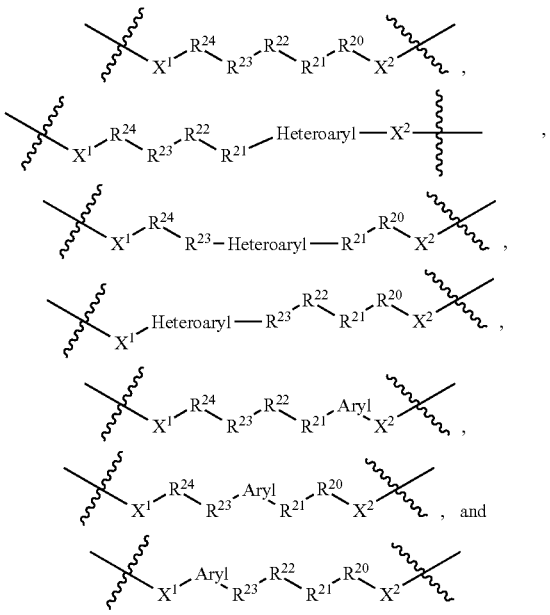
16. The method of claim 1, wherein the cancer is non-Hodgkin's lymphoma.

17. The method of claim 1, wherein the cancer is sarcoma.

18. The method of claim 1, wherein the cancer is synovial sarcoma.

19. The method of claim 1, wherein the cancer is Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, or myosarcoma.

20. The method of claim 1, wherein the Linker is:



wherein:

X^1 and X^2 are independently selected from bond, NH, NR^{25}, CH_2, CHR^{25}, $C(R^{25})_2$, O, and S;

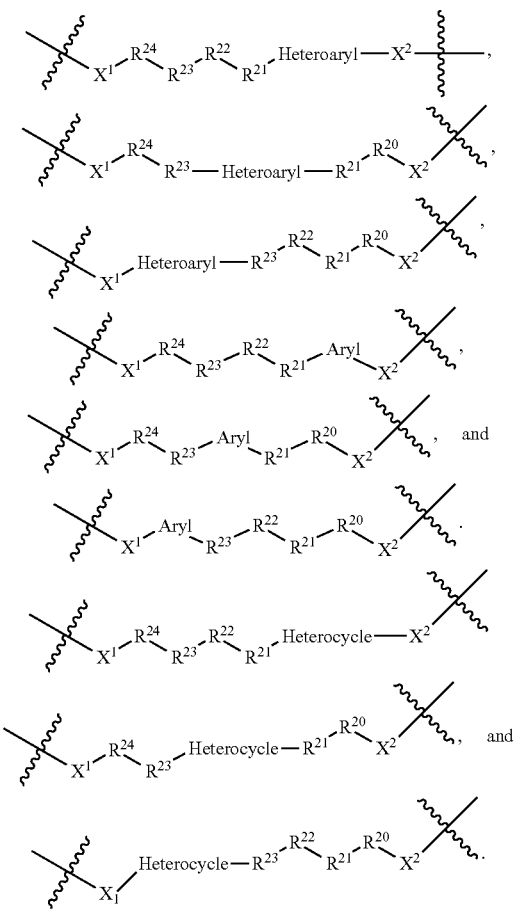
R^{20}, R^{21}, R^{22}, R^{23}, and R^{24} are independently selected from heteroarylalkyl, aryl, arylalkyl, heterocycle, aliphatic, heteroaliphatic, heteroaryl, polypropylene glycol, lactic acid, glycolic acid, carbocycle, bond, alkyl, —C(O)— —C(O)O—, —OC(O)—, —C(O)alkyl, —C(O)Oalkyl, —C(S)—, —SO_2—, —S(O)—, —C(S)—, —C(O)NH—, —NHC(O)—, —N(alkyl)C(O)—, —C(O)N(alkyl)-, —O—, —S—, —NH—, —N(alkyl)-, —CH(—O—R^{26})—, —CH(—NHR^{25})—, —CH(—NH_2)—, —CH(—NR^{25}_2)—, —C(—O—R^{26})alkyl-, —C(—NHR^{25})alkyl-, —C(—NH_2)alkyl-, —C(—NR^{25}_2)alkyl-, -alkyl(R^{27})-alkyl(R^{28})—, —C($R^{27}R^{28}$)—, —P(O)(OR^{26})O—, —P(O)(OR^{26})—, —NHC(O)NH—, —N(R^{25})C(O)N(R^{25})—, —N(H)C(O)N(R^{25})—, polyethylene glycol, poly(lactic-co-glycolic acid), alkene, haloalkyl, alkoxy, and alkyne,

R^{25} is selected at each instance from alkyl, —C(O)H, —C(O)OH, —C(O)alkyl, —C(O)Oalkyl, alkenyl, and alkynyl;

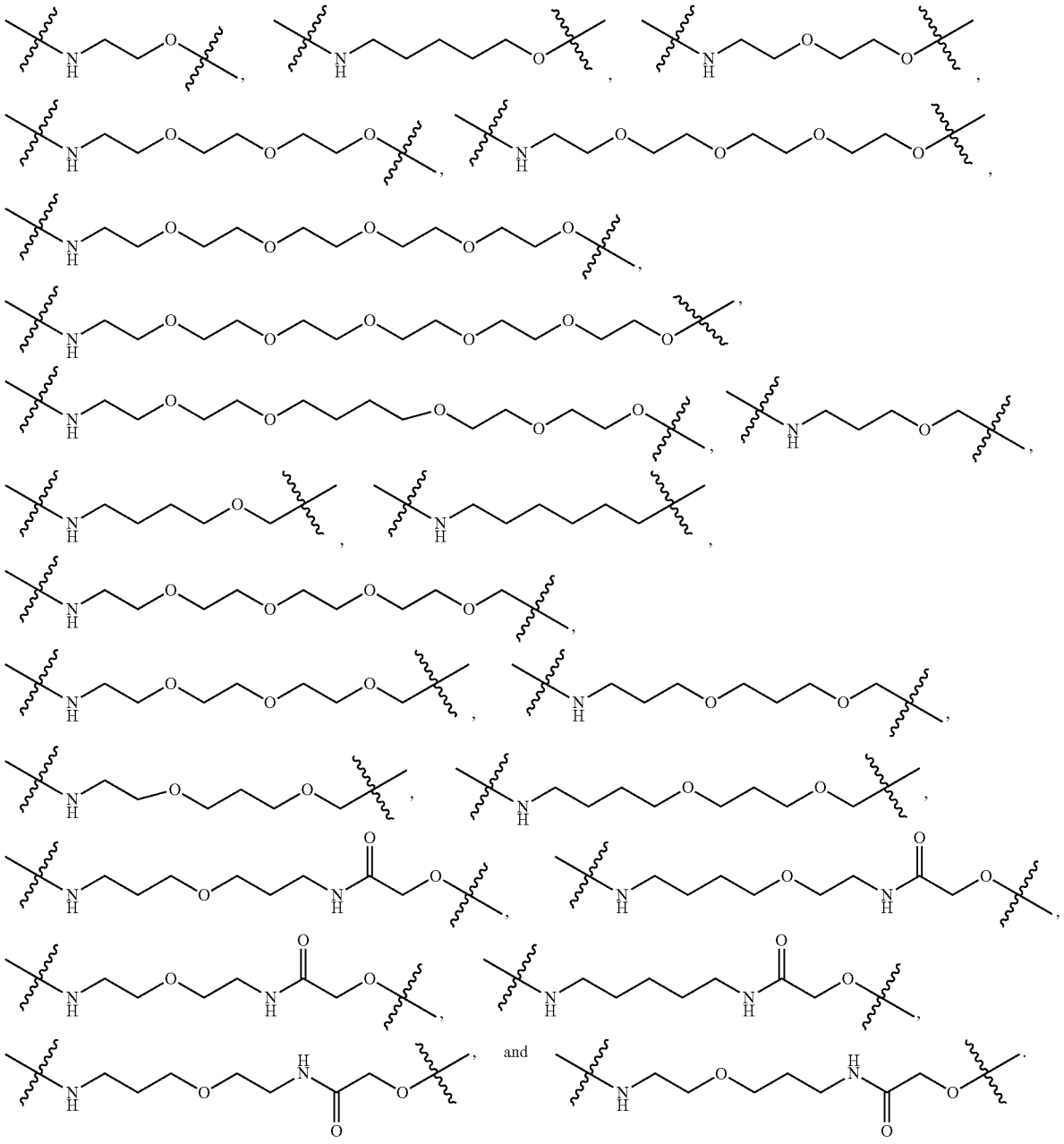
R^{26} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkene, alkyne, aryl, heteroaryl, heterocyclic, aliphatic, or heteroaliphatic; and

R^{27} and R^{28} are independently selected from hydrogen, alkyl, amine, or together with the carbon atom to which they are attached, form C(O), C(S), C=CH_2, a C_3-C_6 spirocarbocycle, or a 4-, 5-, or 6-membered spiroheterocycle comprising 1 or 2 heteroatoms selected from N and O.

21. The method of claim 20, wherein the Linker is selected from:



22. The method of claim 20, wherein the Linker is selected from:



and

23. The method of claim 1, wherein the compound is administered as a solid pharmaceutical composition.

24. The method of claim 1, wherein the compound is administered parenterally.

25. The method of claim 1, wherein the compound is administered intravenously.

26. The method of claim 1, wherein the compound is administered orally.

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